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Interconversion of Bicyclo[2.2.1]hept-2-yne and 5-Bicyclo[2.1.1]hexylidenecarbene

John C. Gilbert* and Jiandong Yin

Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station A5300, Austin, Texas 78712

jgilbert@mail.utexas.edu

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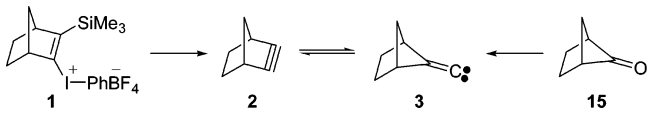
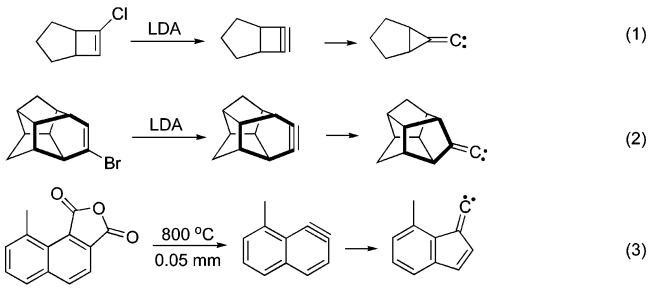


This work provides unambiguous results for the full equilibration of cycloalkyne **2** with its isomeric ring-contracted vinylidene **3** prior to their reaction with 2,3-dihydropyran (**4**), as evidenced by the products formed when **2** and **3** are produced directly from their precursors having bicyclo[2.2.1]heptyl and bicyclo-[2.1.1]hexyl skeletons, respectively.

Introduction

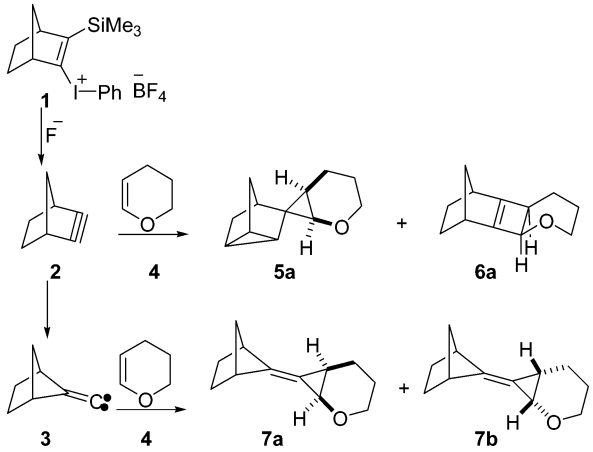
The possible intermediacy of bicyclo[2.2.1]hept-2-yne (norbornyne, **2**) from a bicycloheptene precursor was first claimed by Gassman's group.[1] We recently reported preliminary evidence that **2**, as derived from the bicycloheptyl iodonium salt **1**, isomerizes to 5-bicyclo[2.1.1]hexylidenecarbene (**3**, Scheme 1).[2] Thus, in addition to the major products **5a** and **6a**, minor products **7ab** were formed from the reaction of 2,3-dihydropyran (**4**) with **2**. Formation of the adducts **7ab** could be rationalized most economically through conversion of **2** to **3**.[2,3]

The proposed ring contraction of **2** to **3** has some precedent in the field of cycloalkyne chemistry, as seen in eqs 1−3.[4−6]



Nucleophilic trapping products having both the bicyclo[3.2.0]-heptyl and bicyclo[3.1.0]hexyl skeletons were observed in the first case,[4] but a key labeling experiment confirming the intervention of the cycloalkyne is yet to be reported. In the second example, only the vinylidene was trapped, although a ^{13}C-labeling experiment resulted in the scrambling of the label as would be expected if the cycloalkyne was formed as an intermediate.[5] This result indicates that the cycloalkyne and the carbene may not equilibrate, although it also may simply be a consequence of a kinetic preference for reaction of the carbene

SCHEME 1



(1) (a) Gassman, P. G.; Valcho, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 4768−4770. (b) Gassman, P. G.; Gennick, I. *J. Am. Chem. Soc.* **1980**, *102*, 6863−6864.

(2) Laird, D. W.; Gilbert, J. C. *J. Am. Chem. Soc.* **2001**, *123*, 6704−6705.

(3) (a) Bachrach, S. M.; Gilbert, J. C.; Laird, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 6706−6707. (b) Kinal, A.; Piecuch, P. *J. Phys. Chem. A* **2006**, *110*, 367−378.

(4) Baumgart, K.-D.; Szeimies, G. *Tetrahedron Lett.* **1984**, *25*, 737−740.

(5) Marchand, A. P.; Namboothiri, I. N. N.; Ganguily, B.; Bott, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 6871−6876.

(6) Cioslowski, J.; Piskorz, P.; Moncreiff, D. *J. Am. Chem. Soc.* **1998**, *120*, 1695−1700.

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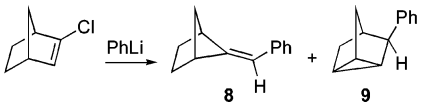
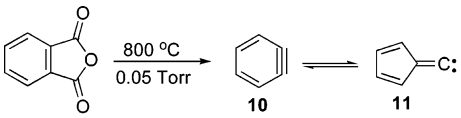
with the trapping agent, cyclohexene, chosen for the investigation. In the third case, only product from trapping of the vinylidene was obtained.[6] Therefore, neither the intermediacy of the alkyne nor its equilibration with ring-contracted vinylidene was proven.

In another report from the Gassman group, treatment of 2-chloronorbornene with phenyllithium was found to afford **8** and **9** (eq 4), but the intermediacy of 2-phenylnorbornyne was not suggested by the authors.[7]

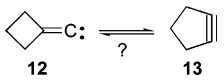


(4)

A true interconversion of a cycloalkyne and its ring-contracted alkylidenecarbene was observed with *o*-benzyne (**10**) and cyclopentadienylidenecarbene (**11**) in 1984 (eq 5).[8] Although the existence of this interconversion was questioned by Wentrup's group in 1988,[9] conclusive proof of this process was furnished by Brown and Eastwood in 1993.[10] However, their results did not show that **10** and **11** fully equilibrate before being trapped by **10** itself. Finally, cyclobutylidenecarbene (**12**) ring expands to cyclopentyne (**13**),[11,12] but the reverse process remains unreported, regardless of whether precursors to either **12** or **13** are used. The present paper provides unambiguous evidence for equilibration of a cycloalkyne with its isomeric ring-contracted vinylidene, as evidenced by the products formed when **3** is produced directly from a precursor having the bicyclo-[2.1.1]hexyl skeleton.



(5)

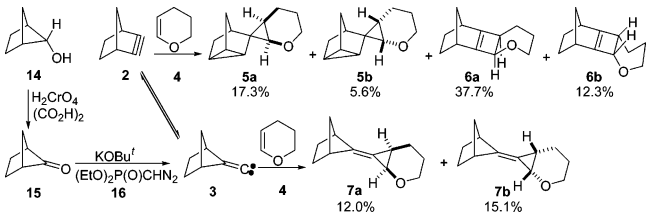


(6)

Results and Discussion

Bicyclo[2.1.1]hexan-5-one (**15**), which could be prepared by oxidation of *endo*-bicyclo[2.1.1]hexan-5-ol (**14**)[13] by known procedures,[14] was selected as the precursor to alkylidenecarbene **3**. Base-promoted reaction of **15** and diethyl (diazomethyl)-phosphonate (**16**)[15] in the presence of dihydropyran **4** (Scheme 2) afforded a mixture of six isomeric products having a *m*/*z* of 176, as shown by GC/MS. This is the *m*/*z* expected for a 1:1 adduct of **2**/**3** and **4**. Analysis of the isomers by ^{1}H and ^{13}C NMR spectroscopy showed that four of the products were identical to those of **5a**, **6a**, and **7ab**.[2]

SCHEME 2

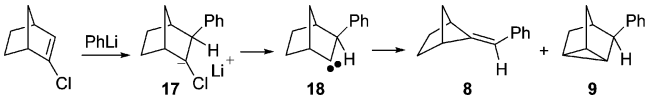


The fifth product could only be isolated as one of the minor components of a mixture containing **6a**. Nonetheless, spectral data allowed its assignment as **6b** based on the following analysis. A distinctive doublet at δ 4.14 ppm (1H), a doublet of triplets (dt) at δ 4.08 ppm (1H), and a doublet of doublets of doublets (ddd) at 3.56 ppm (1H) are comparable to resonances in **6a**, which has a doublet at δ 4.21 ppm (1H), a dt at δ 3.91 ppm (1H), and a ddd at 3.68 ppm (1H). These doublets are assigned to the proton that is both allylic and α to the oxygen atom in the diastereomers **6ab**, whereas the dt and ddd are associated with the other two protons α to the oxygen atom. Unfortunately, ^{13}C NMR spectroscopy provided no additional proof for the structure of **6b** because the resonances for its olefinic carbon atoms were apparently degenerate with those of **6a**. Spectroscopic data could not be obtained for the sixth isomer because of its low yield, but it is tentatively assigned as **5b**, a diastereomer of **5a**. If this is the case, all six possible 1:1 adducts between **2**/**3** and **4** have been formed.

The discrepancy in the number of products produced from this reaction and that reported when iodonium salt **1** was used as the precursor to **2**[16] prompted reinvestigation of the latter reaction. Treatment of **1** with TBAF in the presence of dihydropyran **4** resulted in a mixture whose analysis by GC/MS revealed the presence of six isomers with $m/z = 176$, in addition to other byproducts.[17] The retention times of these isomers were identical to those of the six 1:1 adducts obtained starting with **15** (Scheme 2), and this was confirmed by coinjection of the product mixtures obtained from the two starting materials **1** and **15**. As provided in Table 1, the percentages of the six isomers obtained from the two precursors were not identical.[18]

The data show that the combined yield of **5ab** and **6ab** is 71.8 $\pm$ 1.1%, independent of whether **1** or **15** was used. Given the core [2.2.1] skeleton of products **5** and **6** and the [2.1.1]

(7) Gassman, P. G.; Atkins, T. J. *J. Am. Chem. Soc.* **1970**, *92*, 5810−5811. In their paper, the authors proposed formation of **17**, which led to a carbenoid species **18**. Ring contraction would afford **8**, whereas intramolecular C−H insertion would give rise to **9**.



(8) Barry, M.; Brown, R. F. C.; Eastwood, F. W.; Gunawardana, D. A.; Vogel, C. *Aust. J. Chem. Soc.* **1984**, *37*, 16430-1657.

(9) Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* **1988**, *110*, 1874−1880.

(10) Brown, R. F. C.; Eastwood, F. W. *Synlett* **1993**, 9−19.

(11) (a) Fitjer, L.; Kliebisch, U.; Wehle, D.; Modaressi, S. *Tetrahedron Lett.* **1982**, *23*, 1661−1664. (b) Fitjer, L.; Modaressi, S. *Tetrahedron Lett.* **1983**, *24*, 5495−5498.

(12) (a) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1983**, *105*, 664−665. (b) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 1885−1886. (c) Gilbert, J. C.; McKinley, E. G.; Hou, D.-R. *Tetrahedron* **1997**, *53*, 9891−9902. (d) Gilbert, J. C.; Hou, D.-R.; Grimme, J. W. *J. Org. Chem.* **1999**, *64*, 1529−1534.

(13) (a) Meinwald, J.; Chapman, R. A. *J. Am. Chem. Soc.* **1968**, *90*, 3218−3226. (b) Della, E. W.; Elsey, G. M.; Skouroumounis, G. *Aust. J. Chem.* **1990**, *43*, 1231−1244.

(14) (a) Muller, P.; Blanc, J. *Helv. Chim. Acta* **1979**, *62*, 1980−1984. (b) Krumpolc, M.; Rocek, J. *Org. Synth.* **1981**, *60*, 20−25.

(15) Seyferth, D.; Marmar, R. M.; Hilbert, P. H. *J. Org. Chem.* **1971**, *36*, 1379−1386.

(16) Only four adducts, viz., **5a**, **6a**, and **7ab**, were identified previously.[2]

(17) The nature of these side products is the subject of a manuscript in preparation.

(18) The absolute yield of the six adducts obtained from **1** was not determined in this paper but would be close to 10% according to ref 2, whereas that from **15** was 10% as shown in the Experimental Section. No starting precursors **1** or **15** could be recovered from these two reactions. We believe that most of the other 90% of the mass balance was lost because of decomposition or polymerization of the reactive intermediates.

TABLE 1. Ratios and Percentages of Cycloadducts

	percent[a]		ratios	
adducts	precursor **1**	precursor **15**	precursor **1**	precursor **15**
5a	23.6	17.3	6.5	3.1
5b	3.6	5.6	1.0	1.0
6a	27.6	37.7	7.6	6.8
6b	15.9	12.3	4.4	2.2
7a or **b**	17.8	12.0	4.9	2.2
7b or **a**	11.5	15.1	3.2	2.7

[a] The percent error is estimated to be no more than ±1.5%.

skeleton of **7ab**, it is most reasonable to posit that the major set of isomers **5**/**6** is derived from **2**, with **7** arising from **3**. The near identity in yields of the two categories of bicyclic products is noteworthy and suggests that not only **2** and **3** interconvert but also, remarkably, they appear to achieve complete equilibrium *prior* to undergoing intermolecular reaction. In this scenario, the variances in yields of individual isomers, as a function of the precursor used, could be associated with differences in solvation of the reactive intermediates. Because we have no knowledge of the relative rates of intermolecular reaction of **2** and **3**, it is not possible to draw any conclusions regarding K_{eq} for these two reactive intermediates.

Conclusion

This investigation, in combination with that reported earlier,[2] clearly establishes that cycloalkyne **2** and carbene **3** interconvert. Indeed, the data support the proposition that equilibration of these two intermediates is faster than their reaction with dihydropyran **4**. The demonstrated equilibration is unprecedented for a potential energy hypersurface on which a cycloalkyne and its isomeric vinylidene reside. Moreover, it illustrates the fallibility of extending conclusions based on theoretical calculations in monocyclic systems to their bi- or polycyclic relatives: Thus, the calculations of Johnson and Daoust predict that the ring contraction of cyclopentyne and cyclohexyne to their isomeric carbenes is *endothermic* by 8 and 17 kcal/mol, respectively, with the corresponding enthalpies of activation being 12−23 and 28−41 kcal/mol.[19] Given the conditions under which **2** and **3** generated in our hands, it seems clear that bicyclo[2.2.1]hept-2-yne (**2**), which can be viewed as either a bicyclic cyclopentyne or cyclohexyne, and its companion bicyclo[2.1.1]hexylidenecarbene (**3**) must not be separated by the enthalpic barriers associated with their monocyclic analogues. The experimental results from this paper are in full agreement with theoretical calculations, in which the cycloalkyne **2** is predicted to be 4.0 kcal mol^{-1} higher in energy than the carbene **3**, with the activation energy for converting **3** to **4** being only 2.8 kcal mol^{-1}.[3]

Experimental Section

Materials. Reactions involving anhydrous conditions were carried out under a positive atmosphere of Ar or N_2. Syringes, needles, cannulae, and reaction flasks for the anhydrous reactions were oven-dried and cooled in a desiccator. Diethyl ether and THF were distilled under N_2 from sodium benzophenone ketyl. Dichloromethane was freshly distilled over CaH_2. Flash chromatography was carried out as described[20] on silica gel of 40-μm particle size. Organic extracts were dried over $MgSO_4$. Concentration of solutions refers to the removal of the solvent by rotary evaporation at water aspirator pressures. Quantitative gas chromatograph (GC) was conducted with a flame-ionization detector (FID)[21] and a 30-m × 0.32-mm ID × 0.25 μm HP-5 (cross-linked 5% phenylmethyl siloxane) capillary column and interfaced with a PC running the HP GC ChemStation software. Programmed GC conditions for the analysis were as follows: Carrier gas, helium with a flow rate of 0.9 mL/min; temperature (initial), 50 °C (2 min); ramp 1, 3 °C/min to 150 °C; ramp 2, 20 °C/min to 260 °C; temperature (final), 260 °C (2 min). GC/MS analysis was conducted on a GC equipped with an HP-5 M.S. (cross-linked 5% phenylmethyl siloxane) capillary column (30-m × 0.25-mm ID × 0.25 μm), interfaced with a mass spectrometer. Programmed GC conditions were the same as the above with the exception that the flow rate of the helium was 2.0 mL/min. High-resolution MS analyses were obtained in the chemical ionization (CI) mode. Nuclear magnetic resonance spectra were recorded using spectrometers operating at 300, 400, or 500 MHz for ^{1}H and at 75, 100, or 125 MHz for ^{13}C, respectively. All chemical shifts were measured relative to $CDCl_3$, the solvent for NMR analyses.

General Procedure for the Trapping Reactions. For the trapping reactions involved with the iodonium salt **1**, a 10-mL flask, equipped with a magnetic stir bar, was purged with Ar or N_2 for 5 min before CH_2Cl_2 (2 mL) and dihydropyran **2** (0.62 mL, 6.8 mmol) were added via syringe. The solution was then stirred and cooled to − 78 °C for 10 min, and the iodonium salt **1** (28.0 mg, 0.0614 mmol) in CH_2Cl_2 (3 mL) was added dropwise via cannula at this temperature. The resulting mixture was then stirred for 15 min before being warmed to 0 °C over a period of 1 h. A saturated solution of sodium tetrafluoroborate (3 mL) was added to the above reaction mixture and stirred for an additional 15 min at 0 °C. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with H_2O (3 × 10 mL) and brine (10 mL), then dried and concentrated to give a pale yellow oil, which was analyzed by both GC/MS and quantitative GC.

For the trapping reactions involved with the ketone **15**, KOBu^t (728.6 mg, 6.493 mmol) was quickly weighed into a 10-mL flask, equipped with a magnetic stir bar. After the flask was purged with Ar or N_2 for 5 min, THF (2 mL), diethyl (diazomethyl)phosphonate (**16**, 1.1564 g, 6.492 mmol), and dihydropyran **2** (2.44 mL, 25.94 mmol) were added via syringe. The mixture was then stirred and cooled to −78 °C for 10 min before the ketone **15** (312.0 mg, 3.24 mmol) in THF (3 mL) was added dropwise via cannula at this temperature. The resulting mixture was then stirred for 15 min before the cold bath was removed. The yellowish color of the mixture turned to brown, accompanied by extensive bubbling due to release of the nitrogen gas over a period of 2−10 min. The mixture was further stirred at 25 °C for 30 min. The brown color of the mixture became darker and darker. Water (5 mL) was added dropwise at 0 °C, and the mixture was transferred to a separatory funnel. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with H_2O (3 × 10 mL) and brine, then dried and concentrated. The resulting residue was then subjected to analytical GC. The retention times (min) for the six isomers are: **5a**, 17.93; **6a**, 18.12; **6b**, 18.35; **7a** or **b**, 18.86; **5b**, 19.07; **7b** or **a**, 19.92. Flash chromatography (5% EtOAc/hexanes, R_f = 0.49, 0.44, 0.38) of the residue provided a mixture containing six isomers (56.9 mg, 0.323 mmol, 10%) as a colorless oil. Further purification of this mixture by column chromatography afforded partial separation. Examination and comparison of the spectra of these mixtures with

(19) Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1995**, *117*, 362−367.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(21) It was assumed that all products from the reactions have the same response in the FID, though this has not been justified.

(22) Wiberg, K. B.; Lowry, B. R.; Nist, B. J. *J. Am. Chem. Soc.* **1962**, *84*, 4, 1594−1597.

those in the literature[1] allowed the assignments for the five isomers described in the text.

***endo*-5-Bicyclo[2.1.1]hexanol (14).** The ^{1}H NMR spectrum agreed with that reported by Wiberg et al.[22] ^{13}C NMR: δ 69.8, 42.6, 27.8, 21.5.

Bicyclo[2.1.1]hexan-5-one (15). The ^{1}H NMR spectrum was identical with that given by Wiberg et al.[22] ^{13}C NMR: δ 199.7, 54.4, 27.4, 20.9.

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