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Generation and Trapping of *N*-Substituted-3-azetidinylidenecarbenes

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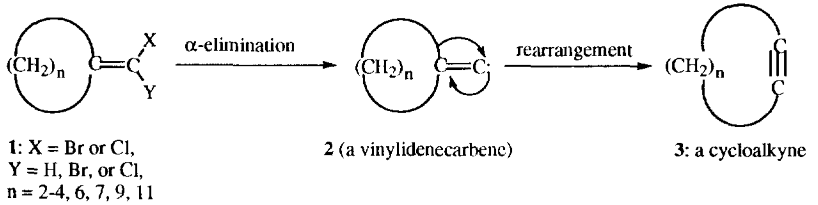
Abstract. The reactive intermediates produced via base-promoted reactions of *N*-tosyl- and *N*-benzhydrylazetidin-3-one (**8a** and **8b**, respectively) with diethyl diazomethylphosphonate (DAMP) have been shown to be vinylidenecarbenes rather than the corresponding cycloalkynes. Thus, *N*-tosylazetidin-3-ylidenecarbene (**9a**) was trapped *in situ* by cyclohexene to afford a cycloadduct, *N-p*-toluenesulfonyl-2-(7'-bicyclo[4.1.0]heptanylidene)azetidine (**10**), whose structure subsequently was established unequivocally via single crystal X-ray structural analysis. These results contrast with that reported previously for the corresponding carbocyclic system (i. e., cyclobutanylidenecarbene-cyclopentyne); in the carbocyclic system, the cycloalkyne (rather than the vinylidenecarbene) is trapped *in situ* . The results of semi-empirical MO calculations (AM1 Hamiltonian) for ring expansion of azetidinylidenecarbenes to azacyclopentynes offer clues to the observed difference between the behavior of the heterocyclic and carbocyclic systems. Copyright © 1996 Elsevier Science Ltd

Recently, cycloalkylidenecarbene-cycloalkyne rearrangements have been the subject of extensive experimental[1,2] and theoretical investigations.[3] Thus, α–elimination of Br_2 from dibromomethylenecyclobutane (**1**, X = Y = Br, n =3) results exclusively in formation of cyclopentyne. When this reaction is performed in the presence of an alkene, [2 + 2] cycloaddition occurs with concomitant formation of a substituted cyclobutene.[1] However, in the case of **1** (n = 4), the corresponding reaction proceeds via an intermediate vinylidenecarbene (**2**, n = 4), which can be trapped *in situ* by cyclohexene to afford a substituted *exo*-methylenecyclpropane.[2] Similarly, we recently reported[4] that 8-(dibromomethylene)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**4**, Scheme 2) reacts with *n*-BuLi-THF to produce the corresponding vinylidenecarbene, **5a**.

Scheme 1

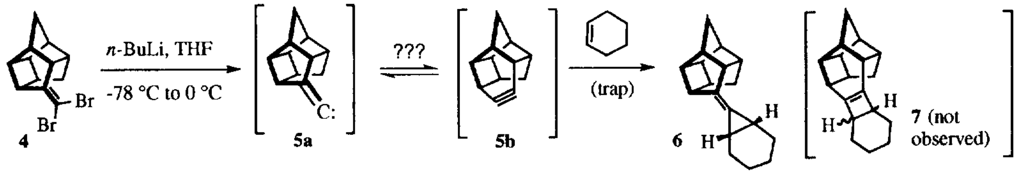


1: X = Br or Cl,
Y = H, Br, or Cl,
n = 2-4, 6, 7, 9, 11

2 (a vinylidenecarbene)

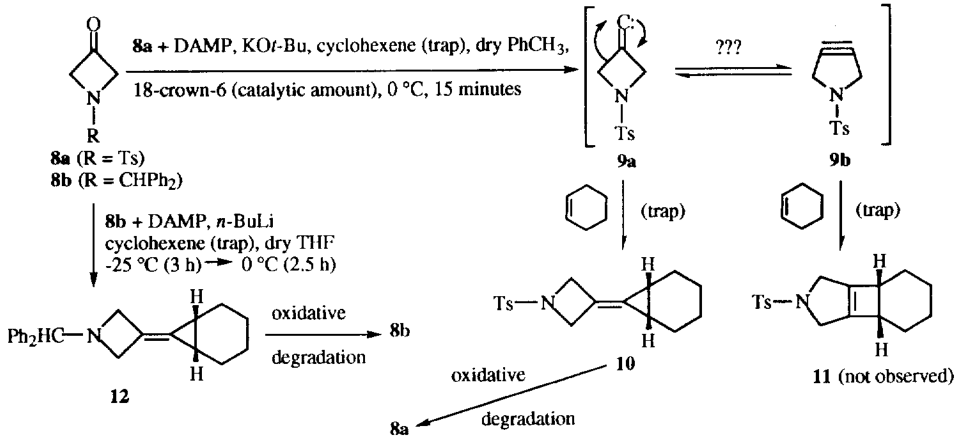
3: a cycloalkyne

Scheme 2



Results and Discussion. In the present study, reactive intermediates were generated via base-promoted reactions of *N*-tosyl- and *N*-benzhydrylazetidin-3-one (**8a**[5] and **8b**,[5,6] respectively) with diethyl diazomethylphosphonate (DAMP).[1c] When performed by using *N*-tosylazetidin-3-one (**8a**) as substrate in the presence of add-ed cyclohexene, a single product, *N*-*p*-toluenesulfonyl-2-(7'-bicyclo[4.1.0]heptanylidene)azetidine (i. e., **10**, mp 81-82 °C) could be isolated in 9% yield. The structure of **10** was established unequivocally via X-ray crystallographic methods.[7] In addition, oxidative degradation of **10**, performed either (i) by using ozone followed by reductive workup with Me_2S or (ii) via reaction of **10** with OsO_4-$NaIO_4$, afforded **8a**.

Scheme 3



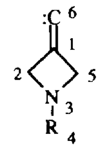
Similarly, reaction of a mixture of **8b** and DAMP[1c] with *n*-BuLi, when performed in the presence of cyclohexene as trap, resulted in the formation of a cycloadduct, *N*-benzhydryl-2-(7'-bicyclo[4.1.0]heptanylidene)-azetidine (**12**) as a colorless, viscous oil (8% yield). Oxidative degradation of **12** with OsO_4-$NaIO_4$ produced **8b**, a result which is consistent with the suggested structure for **12** and with the result described above for oxidative degradation of the corresponding product, **10**, obtained when **9a** was trapped *in situ* by cyclohexene.

Quantum Mechanical Calculations. The results of semiempirical molecular orbital (AM1) calculations[8-10] for a series of vinylidenecarbene-cycloalkyene rearangements which involve species **13-17** are shown in Table 1. These calculations consistently show the ring expansion of **13** to **14** to be endothermic, with ΔH_r° ranging from 5.4–10.6 kcal-mol^{-1}. In contrast, the conversion of **16** to **17** is predicted to be exothermic by about

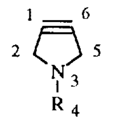
1 kcal/mol.[1d,3b,11] The greater endothermicity of the ring expansion of the aza-analogs, **13**, than of (carbocyclic) carbene **16** is not reflected in the relative activation enthalpies for the transition states of the reaction, all of which are approximately 35 kcal-mol^{-1}. It is possible that the endothermicity of ring expansion of the aza-compounds *vis-à-vis* their carbocyclic analog is associated with the fact that the ring angle C(6)-C(1)-C(2) in **14** shows greater deviation from linearity than does **17** (Table 1).

Since the calculated activation enthalpy for ring expansion appears to be essentially independent of the presence of the nitrogen atom, how can the different chemical fates of carbenes **13** and **16** be explained? The answer to this question may reside in the role entropy could play in defining free energy of activation, $\Delta G^{\neq}$, for the *bi*molecular reaction channels that ultimately determine the structural results. Thus, calculations predict the activation enthalpies, $\Delta H^{\neq}$, for cycloaddition of either **16** or **17** to ethylene are *ca.* 2 kcal-mol^{-1}.[12] Similar values presumably apply to the aza-analogs **13** and **14**, although these have not yet been computed. In both systems, the activation entropy, $\Delta S^{\neq}$, for the bimolecular processes will be negative, with resulting increase in $\Delta G^{\neq}$. This entropic contribution might raise the free energy of the transition state for the cycloaddition processes above that for ring expansion.[13] In this event, the Curtin-Hammett principle[14] becomes applicable and predicts that the dominant reaction channel for the aza-system involves carbene chemistry, whereas that for the all-carbon system reflects cycloalkyne chemistry.[15]

Table 1. Calculated (AM1)[8,9] heats of formation and structural features of **13-17**

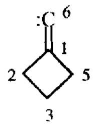


13a: R = H
13b: R = Ts
13c: R = CHPh$_2$

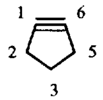


14a: R = H
14b: R = Ts
14c: R = CHPh$_2$

15a: R = H
15b: R = Ts
15c: R = CHPh$_2$



16



17

Compound	$\Delta H_f°$, kcal-mol^{-1} (AM1)	Dihedral Angle[a] 1–2–3–4 (°)	Ring angle 5–1–2 (°)	Ring angle 6–1–2 (°)
13a	152.3	113	88	N/A
14a	160.4	114		113
15a	187.6			
13b	114.3	171	88	
14b	119.7	179		113
15b	149.5			
13c	215.3	119	88	
14c	225.9	126		113
15c	250.9			
16	129.1[b]	N/A	90[b]	
17	128.4[b]	N/A		116[b]

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[a] Dihedral angle involving the specified atoms, in degrees; [b] reference 1d.

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7. Selected X-ray crystallographic data for **10** ($C_{17}H_{21}NO_2S$): Space group: $P2_1/c$; a = 14.6510 (9) Å; b = 9.5057 (6) Å; c = 11.5425 (9) Å; β = 92.242 (6) °; V = 1608.3 (2) Å^3; Z = 4; μ = 1.96 cm^{-1}; D_{calc} = 1.255 g-cm^{-3}; R = 0.0486; R_w = 0.0489. A complete description will be given in the full paper.

8. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902.

9. All computations used the AM1 Hamiltonian with the inclusion of 3x3 configuration interaction (CI). All ground and transition states were verified by means of force constant calculations.[10]

10. Dewar, M. J. S.; Healy, E. F.; Stewart, J. J. P. *J. Chem. Soc., Faraday Trans. 2* **1984**,*3*, 227.

11. An *ab initio* value for this transformation of -4 to -15 kcal/mol has been reported.[3b]

12. Gilbert, J. C.; Kirschner, S. Manuscript in preparation.

13. We recognize that an unrealistically high value of $\Delta S^{\neq}$ is required, so that the $T\Delta S^{\neq}$ factor raises $\Delta G^{\neq}$ for the bimolecular processes above that for the unimolecular ring expansion of carbenes **13** and **16** (Table 1). However, we have noted elsewhere[1a] that AM1 methodologies tend to overestimate the stability of four-membered rings, and thus can predict an excessively high activation barrier for ring expansion.

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15. Incorporation of other heteroatoms at the 4-position of the carbene leads to a range of predicted values for ΔH_r (Kirschner, S. Unpublished results). Experiments to test the computational predictions are planned.

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