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Fused Bicyclic Vinylcyclopropanes from Intramolecular Alkylidene Carbene-Alkene Additions

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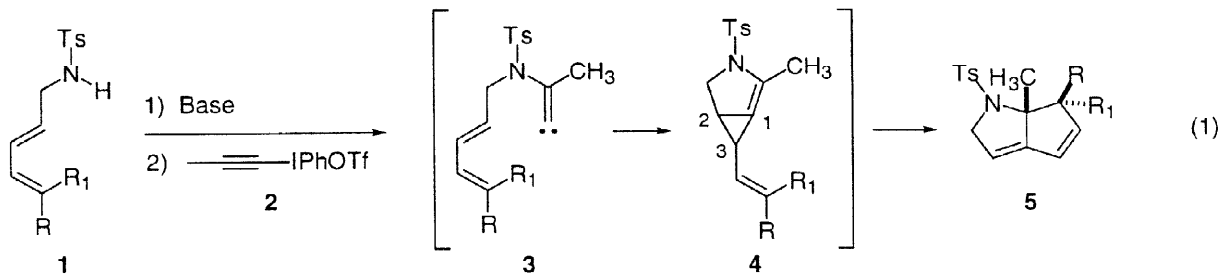
Abstract

A double bond migration driven by the high strain energy of endocyclic methylenecyclopropane-containing fused bicyclic systems is proposed to explain the formation of azabicyclo[3.1.0]hexanes from the intramolecular addition of alkylidene carbenes to alkenes.

Keywords: cyclopropanes; migration

Recently, we reported methodology for cyclopenteneannelated dihydropyrrole synthesis via a complex bond forming cascade[1] initiated by the conjugate addition of a pentadienyl sulfonamide anion to propynyl(phenyl)iodonium triflate **2**, eq. (1).[2] The putative intermediate alkylidene carbene **3** adds intramolecularly to a strategically placed double bond creating a highly strained 3-alkenyl endocyclic methylenecyclopropane **4**.[3] Subsequent homolytic cleavage of the cyclopropyl bond distal to the fused unsaturation site followed by diradical cyclization furnishes the annelated dihydropyrroles **5**. In the course of our studies, we observed that the isomeric isoprenyl substrate **6** does not afford the expected azabicyclo[3.3.0]octene **9**, but rather a compound identified as the exocyclic methylene-containing azabicyclo[3.1.0]hexane **10**, eq. (2). Intrigued by the implication that an alternate reactive pathway is available to 2-alkenyl endocyclic methylenecyclopropanes, we embarked on a study analyzing azabicyclohexane formation from allylic sulfonamides.



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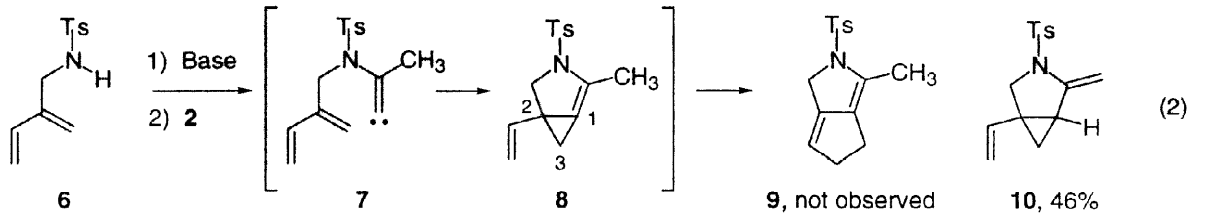
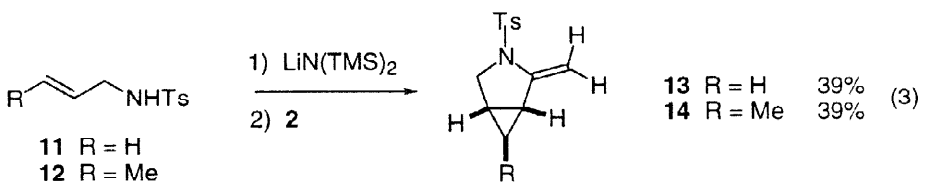
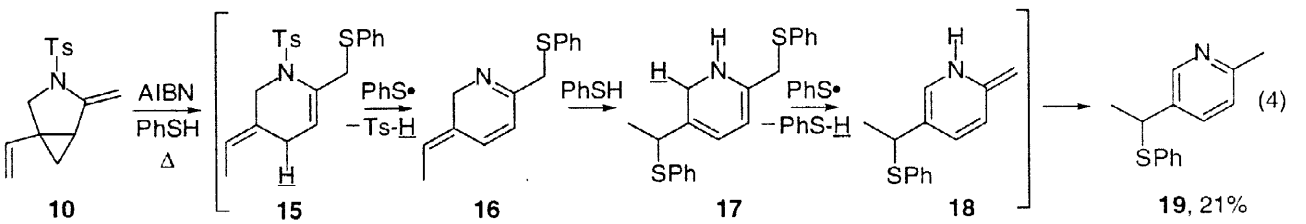


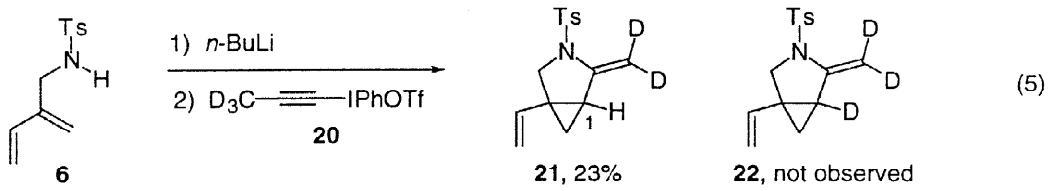
Reaction parameters such as temperature, concentration, time, and reagent stoichiometry were examined in an attempt to maximize the yield of **10** from **6** and **2**. These studies converged on the following conditions for optimal conversion of the allylic tosylamides **6**, **11**, and **12** (eqs. (2) and (3)) into their corresponding vinylcyclopropane derivatives: addition of 1.0 equiv of propynyl(phenyl)iodonium triflate[4] in THF over 15 min to the deprotonated tosylamide in refluxing THF followed by an additional 30 min at reflux. A neutral aqueous quench followed by flash chromatography[5] on deactivated silica gel (4:1 with H_2O by mass) with 6% Et_2O and 1% Et_3N in hexanes afforded the bicyclic systems in 39-46% yields. These species **10**, **13**, and **14** exhibited NMR, IR, and MS spectral data fully consistent with the assigned structures [for **10:** IR ($CDCl_3$) 3090, 1643, 1349, 1167 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.71 (d, J = 8.4 Hz, 2 H), 6.70 (d, J = 8.4 Hz, 2 H), 5.47 (s, 1 H), 5.12 (dd, J = 10.7, 17.3 Hz, 1 H), 4.73 (dd, J = 0.9, 10.7 Hz, 1 H), 4.64 (dd, J = 0.9, 17.3 Hz, 1 H), 4.39 (s, 1 H), 3.76 (s, 2 H), 1.82 (s, 3 H), 1.43 (dd, J = 4.0, 8.2 Hz, 1 H), 0.46 (m, 1 H), -0.49 (m, 1 H); ^{13}C NMR (50 MHz, C_6D_6) δ 145.4, 143.5, 136.8, 136.4, 129.5, 127.5, 113.5, 90.8, 54.8, 31.8, 27.4, 21.1, 17.5; EIMS *m/z* (relative intensity) 275 (M^+, 6), 120 (62), 91 (100); HRMS calcd. for $C_{15}H_{17}NO_2S$: 275.0980, found: 275.0979]. The azabicyclo[3.1.0]hexanes decompose over several days at room temperature in $CDCl_3$ or several months at -15 °C in C_6D_6 to unidentified products. The addition of thiophenol to **10** results in a mixture of products from which pyridine **19** is isolated. A plausible mechanistic course for this complex transformation is shown in eq. (4), although alternative pathways cannot be dismissed.

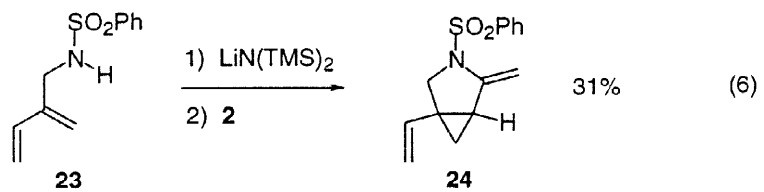




Utilization of trideuterated propynyl(phenyl)iodonium triflate (**16**) in combination with **6** provides insight into the reaction mechanism. The lack of label incorporation at C(1) in **21** suggests that an *inter*molecular proton (or hydrogen) transfer step is responsible for

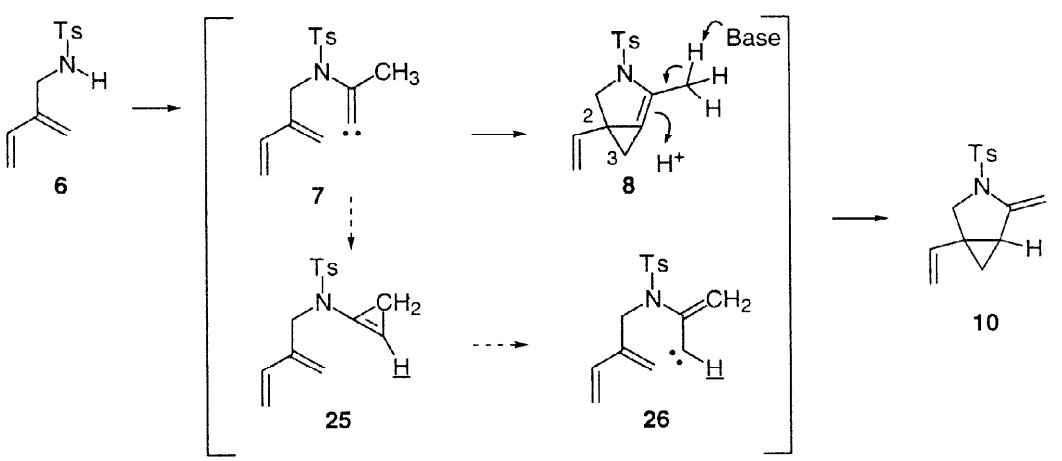
delivering "H" to this carbon, eq. (5). The source of the proton transferred remains elusive, however. Hydrogen/proton donation from solvent is discounted since the combination of **2** with **6** in d_8-THF fails to form any deuterated products. The occurrence of base-driven (tosyl amide anion) cyclopropyl proton exchange in the labeling experiment is excluded as well, since treatment of **21** with $LiN(TMS)_2$ followed by a D_2O quench returns only starting material. Possible intermolecular proton donation by the mildly acidic tosyl methyl group can be eliminated by the successful cyclization of the *benzene*sulfonyl containing species **23**, eq. (6).





Our mechanistic interpretation of these results involves relief of endocyclic methylenecyclopropyl ring strain in the intermediate **8** via base mediated bond migration, Scheme.[6] Apparently, this deprotonation/reprotonation sequence is faster than cyclopropane C-C scission (cf. **4** → **5**) when a radical stabilizing group at C(3) is lacking. The generation of a single anti product **14** from *trans*-2-butenylsulfonamide **12** is consistent with the addition of a singlet alkylidene carbene to an olefin.[7] An alternative 1,3 C-H insertion pathway within **7** to furnish the cyclopropene **25**,[8] which can subsequently rearrange to vinyl carbene **26**[9] en route to the same azabicyclo[3.1.0]hexane product **10**, must be excluded by the observation that no **22** was detected in the labeling study.

Scheme



In summary, the conjugate addition of allylic sulfonamide anions to propynyl(phenyl)iodonium triflate yields azabicyclo[3.1.0]hexanes in moderate yields. It is plausible that relief of the high ring strain energy of the first-formed methylene cyclopropene is provided by double bond migration to yield the exocyclic methylene-containing products.

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