Stereoselective, Intermolecular Dienyltosylamide/ Alkynyliodonium Salt Additions in the Synthesis of Fused Bicyclic Dihydropyrrole Derivatives

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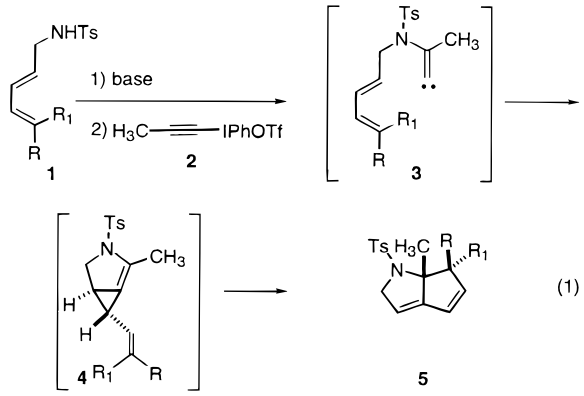
Alkylidene carbenes have been utilized in a variety of C−C bond forming reactions including (1) 1,2-migration to afford functionalized alkynes, (2) insertion into 1,3- and 1,5-disposed C−H bonds to furnish carbocycles and heterocycles, and (3) addition to alkenes to generate methylenecyclopropanes.[1] While these carbenes can be accessed by many methods, the addition of "soft" nucleophiles to alkynyl(phenyl)iodonium salt electrophiles stands out as a particularly mild technique.[2] For example, the intermolecular combination of tosylamide anions with propynyl(phenyl)iodonium triflate and the intramolecular cyclization of functionalized α,ω-tosylamide-alkynyliodonium substrates provide a host of dihydropyrrole derivatives via 1,5-C−H insertion of the intermediate carbene.[3] However, intramolecular alkene addition with such alkylidene carbenes has not been examined. In particular, a variant of this process with 1,3-diene substrates has the potential for generating highly strained, fused, endocyclic 2-vinylmethylenecyclopropanes which offer facile entry into extended diyls related to trimethylenemethane.[4] The subsequent rearrangement chemistry of these diyls may be harnessed for the deliberate construction of complex, functionally rich ring systems of value in organic synthesis. Such 1,2′-bis allyl diradical intermediates more commonly can be accessed from the related but less-activated allylidenecyclopropanes under vigorous thermolysis, and their cyclization to cyclopentene derivatives has been detailed.[5−7] However, the use of readily available alkynyliodonium salts to initiate a cascade which generates this diyl intermediate under comparably mild conditions has not been explored. We capitalize upon the lability of azabicyclo[3.1.0]-hexene derivatives **4**, available through intermolecular combination of simple dienyltosylamides **1** with propynyl(phenyl)-iodonium triflate (**2**), to access these diyls and, ultimately, their rearrangement/cyclization products, the cyclopentenannelated dihydropyrroles **5** (eq 1). Alkylidene carbenes **3** prepared from these substrates harbor only refractory sp^2 1,5 disposed C−H bonds and thus permit the normally slower alkene cycloaddition pathway to compete with C−H insertion.



Preliminary attempts at reducing this concept to practice focused on combining the lithium salt of the (*E*,*E*)-pentadienyltosylamide **1a** (R = Ph, R_1 = H) with the iodonium salt **2**[8] in ethereal solvents. The bicyclic species **5a** (R = Ph, R_1 = H) was isolated as the only characterizable product from this multistep process. No evidence for a plausible regioisomeric product, the bicycle **10** (Scheme 1), or of a product diastereomeric to **5a** was forthcoming. NMR characterization (see the Supporting Information) of an analogue of **5a** (**5e**, vide infra) revealed the general connectivity of the bicyclic framework (HMQC/HMBC) as well as the exclusive syn stereochemistry (dNOE, homonuclear coupling). The isolation of a single stereo- and regiochemically homogeneous bicyclic product was consistently observed as the diene substituent R (R_1 = H) was varied (vide infra). Optimization studies measured the efficiency of bicycle production as a function of solvent (THF, DME, toluene), metal counterion (Li, Na, K), concentration (0.001 M → 0.1 M), reagent ratio, and temperature (−78 °C → refluxing solvent). These studies converged on the following optimal conditions for production of **5a**: addition of 1.5 equiv of iodonium salt **2** dissolved in THF to the deprotonated dienyltosylamide **1a** in refluxing THF over 4 h. Significant quantities (10−20%) of starting dienyltosylamide **1a** can be recovered from the reaction mixture. Additives intended to modulate the reactivity of the free alkylidene carbene **3** (Ph_2S, Ph_3P) had no effect on the course of the reaction.[9]

The chemical nature of the diene terminus substituent R appears to be crucial for reaction efficiency (Table 1). Groups R that effectively stabilize the presumed adjacent radical (cf., Scheme 1) via resonance lead to higher yields of bicyclic product. Thus, benzylic substitution (entry a, R = Ph, R_1 = H and entry b, R = *p*-$(CH_3O)C_6H_4$, R_1 = H) afford the best conversion of substrate to product. The relatively low yield with the electron-deficient *p*-nitrophenyl substituent (entry c) may be a consequence of either a less facile carbene addition to the now electron poor alkene of **3c** or of the emergence of undesired competitive pathways involving conjugate nucleophile addition to the electrophilic

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(9) For an example of intramolecular sulfur ylide formation from an alkylidene carbene, see ref 3j.

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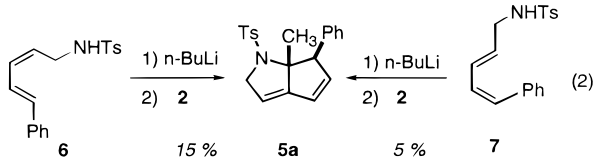
Table 1. Combination of Dienyltosylamides **1** with Iodonium Salt **2** To Furnish Bicyclic Dihydropyrrole Derivatives **5**

entry	amide substr.	R	R_1	bicyclic prod.	yield (%)
a	**1a**	Ph	H	**5a**	58
b	**1b**	*p*-$(CH_3O)C_6H_4$	H	**5b**	51
c	**1c**	*p*-$(O_2N)C_6H_4$	H	**5c**	12
d	**1d**	PhCH=CH	H	**5d**	35
e	**1e**	CH_3	H	**5e**	24
f	**1f**	TMS	H	**5f**	27
g	**1g**	CH_3	CH_3		

nitrostyrenyl moiety of **1c**. Styryl-type stabilization of the putative (di)radical intermediate (cf., **8**, Scheme 1) also promotes bicycle formation (entry d), but not to the extent of an aryl ring. Groups R/R_1 that do not participate in resonance stabilization of an intermediate (di)radical provide bicyclic product in much diminished yields. The simple methyl- (entry e) and trimethylsilyl- (entry f) substituted dienyltosylamides **1e** and **1f**, respectively, afford cyclized product in only ~25% yield in either case. Attempts to combine a terminal *gem*-dimethyl version of **1** (entry g, $R = R_1 = CH_3$) with iodonium salt **2** did not furnish any bicyclic product.

The relationship between starting diene geometry and bicyclic product stereochemistry was probed with the (*Z*,*E*)- and (*E*,*Z*)-dienyltosylamide substrates **6** and **7**, respectively (eq 2). In both cases, application of the optimal reaction conditions with iodonium salt **2** afforded only modest amounts of bicyclic material.

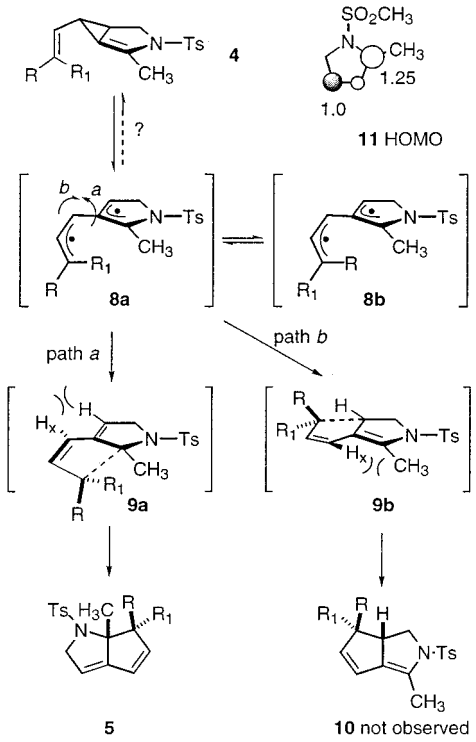


Importantly, this bicyclic material, formed from both **6** and **7**, proved identical in all respects to the bicycle **5a** prepared from the (*E*,*E*)-diene **1a**. Thus, there is no evidence to suggest a direct connection between starting alkene geometry and product stereochemistry. Rather, the stereochemical outcome of cyclization appears to result from mechanistic imperatives.

A mechanistic interpretation of this complex transformation is shown in Scheme 1. Alkylidene carbene addition to the proximal alkene (cf., **3** → **4**) is presumed to precede azabicyclo[3.1.0]-hexene formation. The highly contorted alkene in **4** (≈ a trans double bond in a six-membered ring) is likely to facilitate homolytic fragmentation of the distal cyclopropyl C−C single bond to relieve ring strain. The resultant orthogonal 1,2′-bis allylic diradical **8a** is related to similar diyls generated from thermolysis of allylidene- or vinylmethylenecyclopropanes.[5,6] Recent reports by Cohen[5b] and Cohen and Gajewski[5a] describe the energy surface associated with this reactive intermediate, and application of that analysis to **8a** suggests that cyclization by rotation about the central 1,2′−C−C bond in either direction is feasible. However, only the particular regioisomer formed by counterclockwise rotation about this bond (path *a*) is observed. Both steric and electronic factors may conspire to favor this direction of rotation. Counterclockwise rotation (path *a*) engenders only an H_x−H steric interaction as the radical termini approach bonding distance (cf., **9a**), while the alternative clockwise motion (path *b*) raises a potentially more energetically penalizing H_x−CH_3 steric interaction (cf., **9b**) as the final C−C bond forms. Furthermore, 6-31G**//6-31G**MP2 level calculations[10] on the model allylic radical **11** revealed that the tertiary carbon (where cyclization is observed) bears a higher electron density in the HOMO than does the secondary carbon.[5b]

(10) Geometries were optimized at the unrestricted Hartree−Fock level with the 6-31 G** basis set. Single point energies were calculated at the MP2 level.

Scheme 1



In the Cohen work, alkene geometry in the allylidenecyclopropane was largely preserved upon cyclization to cyclopentene product. In contrast, this information is lost in the present series (cf., **1a** and **7**). A plausible rationale for this observation in indicated in **8a**/**8b**, where equilibration of alkene geometry is faster than diradical collapse. In this scenerio, a common intermediate **9a** ($R = Ph$, $R_1 = H$) from either **1a** ($R = Ph$, $R_1 = H$) or **7** ($R = H$, $R_1 = Ph$) is the precursor to the observed product **5a**. The salient steric interactions which emerge from placing either R or R_1 under the dihydropyrrole ring when the radical termini approach bonding distance clearly should favor the smaller group in this endo position (e.g., **9a**, $R_1 = H$), leading to the observed syn stereochemistry. The discrepancy between these observations and the Cohen work may be traced to a difference in size of the key substituent R_1: R_1 = phenyl in the present study while $R_1 = CH_3$ or SPh in the Cohen work. Thus, in the earlier investigation, cyclization through a diradical species related to **9a** ($R = H$, $R_1 = CH_3$) may compete with allyl radical isomerization, while with the bulkier system **9a** ($R = H$, $R_1 =$ Ph), equilibration may be more rapid.

In summary, addition of simple pentadienyltosylamide derivatives to the two-carbon electrophile propynyl(phenyl)iodonium triflate initiates a sequence of transformations which ultimately forms four new bonds ($1 \times C-N$, $3 \times C-C$) in a single operation and furnishes complex, highly functionalized cyclopentenanne-lated dihydropyrrole products in moderate yields with complete stereoselectivity. This sequence demonstrates that diyls resulting from homolytic scission of alkylidene carbene−alkene adducts can be readily accessed under mild experimental conditions, and that, in the presence of appropriate pendant functionality, these diyls can productively cyclize. Further studies examining the scope and utility of these transformations in organic synthesis are in progress.

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Supporting Information Available: Full spectral data (^1H NMR, ^{13}C NMR, IR, LRMS, HRMS) and copies of ^1H and ^{13}C NMR spectra for **5a**−**f** (23 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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