

INTER- AND INTRAMOLECULAR [4+2] CYCLOADDITION OF NITROALKENES WITH ALLENYLSILANES. A CASE OF UNEXPECTED REGIOSELECTIVITY

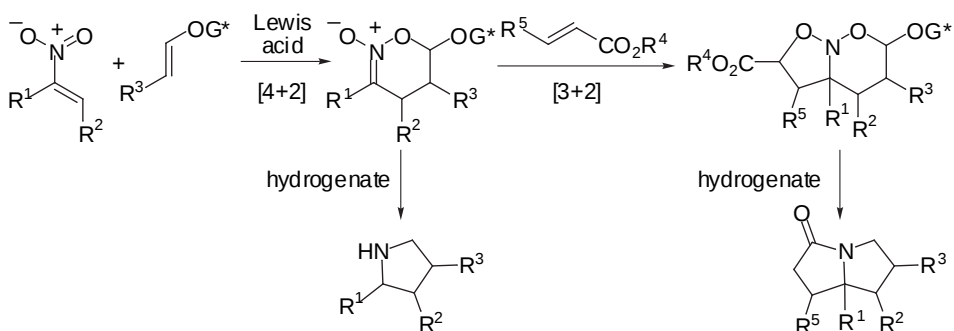
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Abstract- A conjugated nitroalkene tethered to an allenylsilane undergoes formal [4+2] cycloaddition in the presence of tin tetrachloride to afford a bicyclic nitronate. The stereo- and regiochemical course of the reaction was established by a subsequent dipolar cycloaddition with 4-bromophenyl acrylate to generate a crystalline nitroso acetal. Single crystal X-Ray crystallographic analysis of the nitroso acetal revealed an unexpected stereostructure which arose from attack of the nitroalkene on the central carbon of the allenylsilane and closure of the oxygen atom on the terminal carbon. This outcome is interpreted as arising from a stepwise reaction *via* a silicon-stabilized carbocation which can undergo rotation to an allylic cation prior to ring closure. An intermolecular example of this same process was also documented.

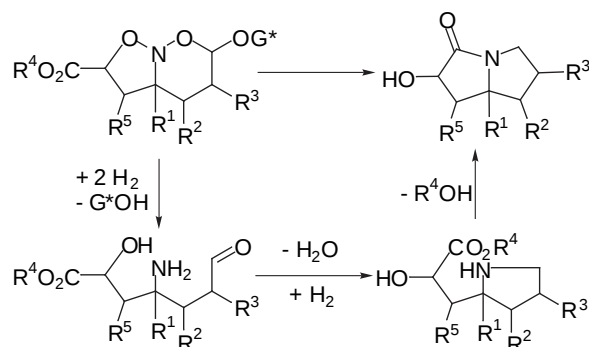
The heterodiene cycloaddition of conjugated nitroalkenes in both inter- and intramolecular modes has proven to be a powerful strategy for the construction of isolated and fused pyrrolidines, respectively.^{1,2} The basic approach illustrated in Scheme 1 involves the combination of a nitroalkene (heterodiene) with an enol ether (dienophile), usually under the action of a Lewis acid to generate a nitronate. This nitronate can undergo hydrogenolytic transformation into a pyrrolidine directly^{3,4} or may first be engaged as a dipole in a [3+2] cycloaddition with a suitable dienophile to generate a nitroso acetal. Hydrogenolysis of the nitroso acetal also produces pyrrolidines of greater structural complexity.^{5,6}

Scheme 1



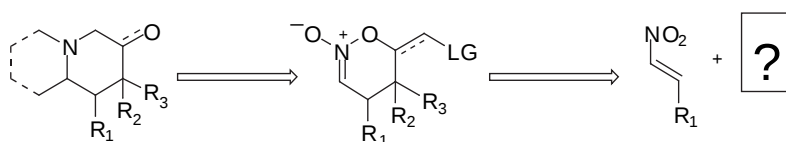
The basis of the pyrrolidine ring formation is the 1,5-relationship of the nitrogen atom and the acetal carbon in either the nitronate or the nitroso acetal. As shown in Scheme 2, hydrogenolysis of the N-O bond and subsequent reduction of the nitrogenous functional group reveals a γ -amino aldehyde which rapidly forms the pyrrolidine *via* condensation and saturation of the intermediate imine. This process constitutes the cornerstone of the entire tandem [4+2]/[3+2] cycloaddition program.

Scheme 2



In the context of our efforts on the total syntheses of a number of indolizidine alkaloids, we developed a procedure to construct a 5,6-fused system by making use of specially designed dipolarophiles that incorporated the additional carbon needed for the larger ring.^{7,8} For a synthetic approach to another family of polycyclic alkaloids, we were interested in developing a general and complimentary method to build a piperidine ring from a suitably functionalized six-membered ring nitronate, Scheme 3. The initial strategy was to adapt a three carbon dienophilic unit that would be capable of inverse-electron-demand [4+2] cycloaddition with a nitroalkene. This dienophile should also carry an appropriate group at the terminus that can activate the critical ring formation by a substitution reaction with the amino group released after hydrogenolysis of the nitronate (or nitroso acetal) to afford the piperidine ring.

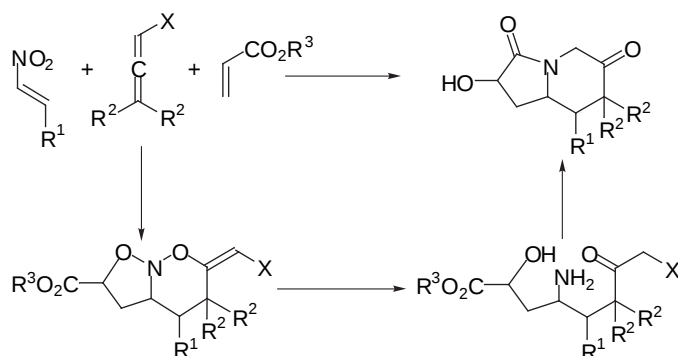
Scheme 3



After considering a number of simple allyl derivatives, we selected to investigate the use of a substituted allene as the dienophile for a number of reasons. Allenes are known to be good participants as both acceptors and donors in [2+2] and [4+2] cycloaddition reactions.^{9,10} The chirality of substituted allenes should give rise to an enantiocontrolled cycloaddition. Moreover, the uniquely packaged three-carbon unit of the allene allows for a number of post-cycloaddition modifications that could lead to suitable electrophiles for the formation of the piperidine ring. Scheme 4 illustrates the transformations of cycloadducts derived from electron-deficient allenes and electron-rich allenes to generate keto-

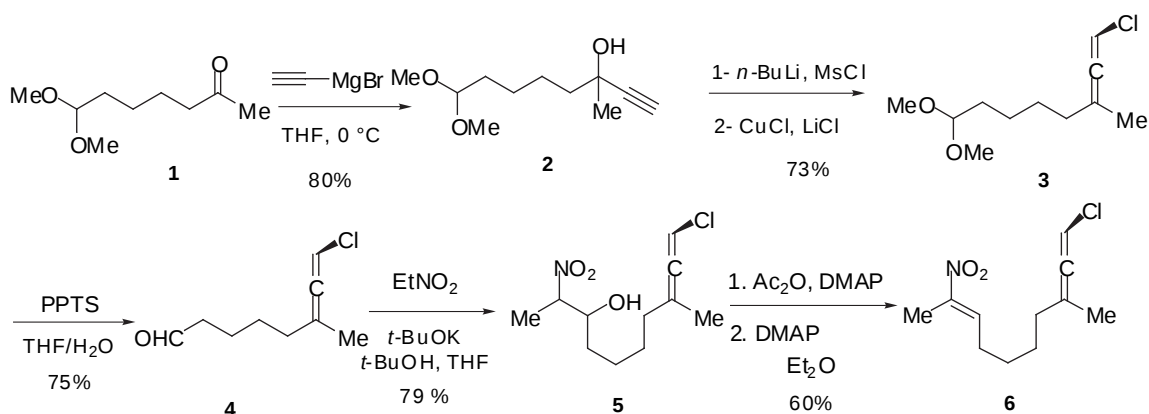
piperidines. Through hydrogenolysis of the exo alkylidene nitronate bearing a nucleofugal group on the terminus, we envisioned the formation of a highly reactive α -halo ketone which should rapidly close to the desired ring. We describe in this communication the first successful cycloadditions of allenylsilanes with nitroalkenes that provided an unexpected and potentially useful ring structure.

Scheme 4



Despite the obvious attenuation of dienophilic character, we first investigated the intramolecular [4+2] cycloaddition of an electron-deficient chloroallene in view of the direct installation of the requisite alkylidene functionality. The synthesis of the precursor nitroalkene is depicted in Scheme 5. Addition of ethynylmagnesium bromide to the methyl ketone (**1**) afforded propargylic alcohol (**2**) in 80% yield. Alcohol (**2**) was converted to a propargylic mesylate which was treated with a solution of LiCuCl_2 in THF (generated by addition of lithium chloride to a solution of CuCl) to produce the corresponding chloroallene (**3**) in 73% yield.¹¹ After hydrolysis of the dimethoxy acetal (**3**), the resulting aldehyde (**4**) was converted to nitroalkene (**6**) by the usual procedure. Base-promoted addition of nitroethane to aldehyde (**4**) afforded the nitro aldol (**5**) as a mixture of diastereomers that was then subjected to dehydration conditions with acetic anhydride and DMAP to generate the nitroalkene (**6**) in 60% yield.

Scheme 5

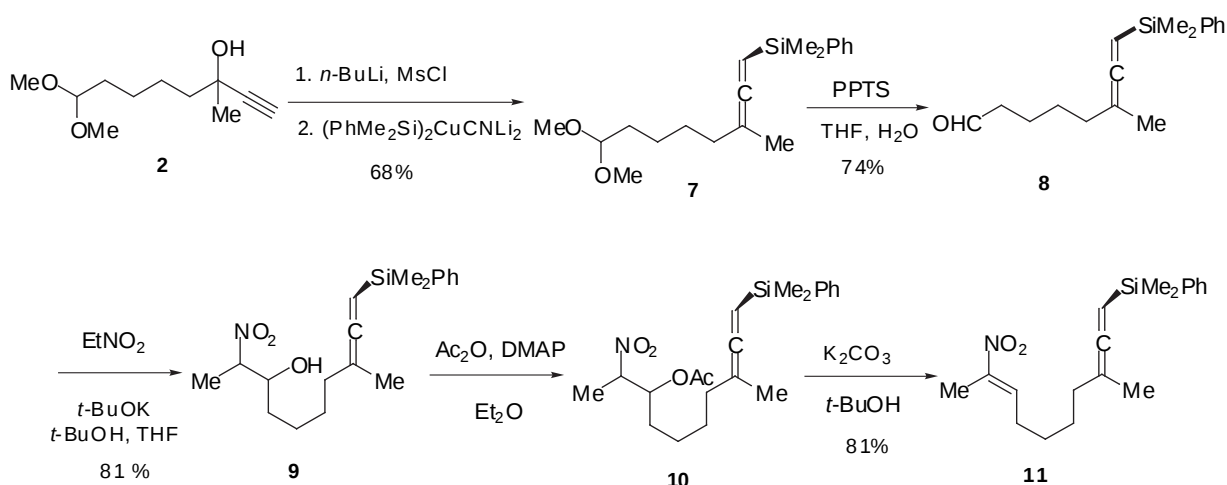


With this nitroalkene in hand, we investigated the ability of the chloroallene dienophile to engage in an inverse-electron demand [4+2] cycloaddition. In the presence of a variety of Lewis acid as well as under

thermal conditions, we were unable to detect any trace of nitronate; in almost all cases, the starting material was recovered.

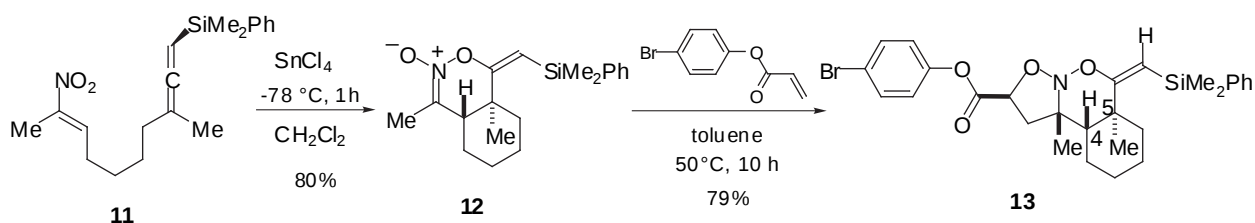
We reasoned that the presence of an electron-withdrawing group rendered the allene unreactive toward the nitroalkene. Accordingly we considered the use of a more electron-releasing substituent, we turned our attention to the preparation and testing of the corresponding allenylsilane (**11**).¹² The synthesis was accomplished in an analogous fashion as for the chloroallene (**6**) above with the aid of a silyl cuprate reagent, Scheme 6. Thus, propargyl alcohol (**2**) was again converted to the mesylate which was treated with the higher order silyl cyanocuprate to afford the allenylsilane (**7**) in 68% yield.¹³ Subsequent deprotection and nitroolefination as before afforded the target nitroalkene substrate without difficulty. In this case, however, the intermediate nitro acetate was isolated and subjected to elimination under more strongly basic conditions.

Scheme 6



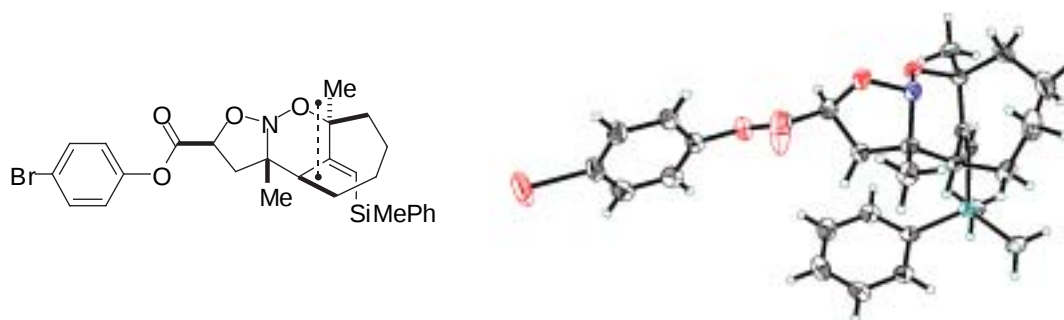
The [4+2] cycloaddition was carried out in the presence of tin tetrachloride for 1 h at -78°C . We were delighted to obtain a nitronate in 80% yield after purification, Scheme 7. The NMR spectra indicated the presence of a single product, but the detailed structure could not be confirmed. Thus, the nitronate (**12**) was treated with 4-bromophenyl acrylate and NaHCO_3 in toluene at 50°C for 10 h. After purification, the tandem intra/inter [4+2]/[3+2] cycloaddition afforded a nitroso acetal (**13**) in 79% yield as a single diastereomer.

Scheme 7



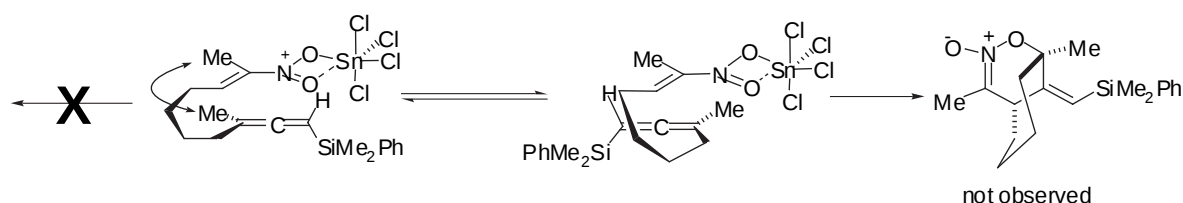
NMR spectral analysis (^1H , ^{13}C , 2D and NOE) of this nitroso acetal was not consistent with the expected structure. For example, **13** displayed an NOE effect between the vinyl proton and the C(4) proton as well as the C(5) methyl that cannot be explained by inspection of a model. Fortunately, we were able to obtain crystals of **13** suitable for X-Ray analysis. An ORTEP image of the final structure is depicted in Figure 1.¹⁴

Figure 1. X-Ray structure of nitroso acetal (**13**).



To our surprise this structure arises from a *reversed* regioselectivity in the intramolecular [4+2] cycloaddition. Inspection of molecular models reveals that folding of the sidechain in the expected orientation as depicted in Scheme 8 engenders an unfavorable steric interaction between the two methyl groups. To avoid this interaction, the side chain could fold in a different orientation, but the models suggest that a concerted cycloaddition in this mode is geometrically not feasible as it leads to a highly strained bicyclic system which is isomeric to the observed product.

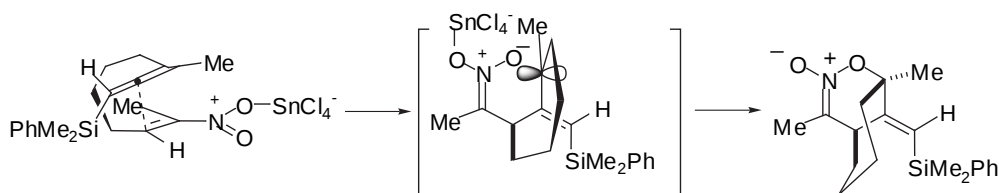
Scheme 8



To explain the regio- and stereochemical course of cycloaddition, we surmise that the allene reacted through electrophilic attack of the nitroalkene on the central carbon of the allene to generate a carbocation which can then collapse to form the nitronate by closure of the nitro oxygen onto the terminal carbon. Of the various mechanistic hypotheses that can be considered, we suggest, on the basis of significant literature precedent, that the activated nitroalkene attacks the β - γ double bond of the allenylsilane to generate a tertiary carbocation as shown in Scheme 9.¹⁵ This species then collapses to form the O-C bond and generate the corresponding nitronate. However, since the π -orbitals of the allene are perpendicular to one another, in the initially formed allyl cation, the $p(\text{C}^+)$ and $\pi(\text{C}=\text{C})$ orbitals are also perpendicular, and a 90° rotation around the C-C bond is necessary for achieving the allylic stabilization. Also, to

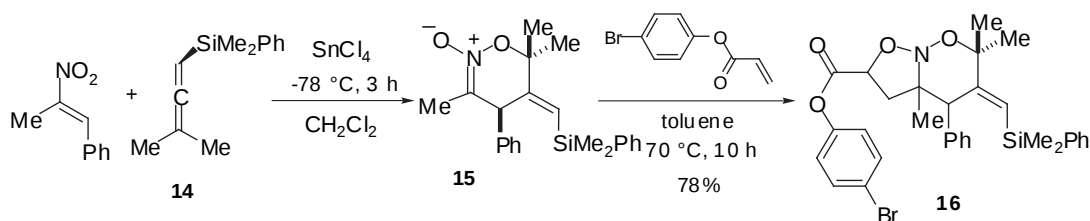
generate the observed *E* vinylsilane geometry, the nitroalkene must approach *syn* to the silicon on the allenylsilane.¹⁶ It is well established that electrophilic attack at allenes often occurs to produce the *Z*-alkenes as guided by formation of the more stable carbocation.

Scheme 9



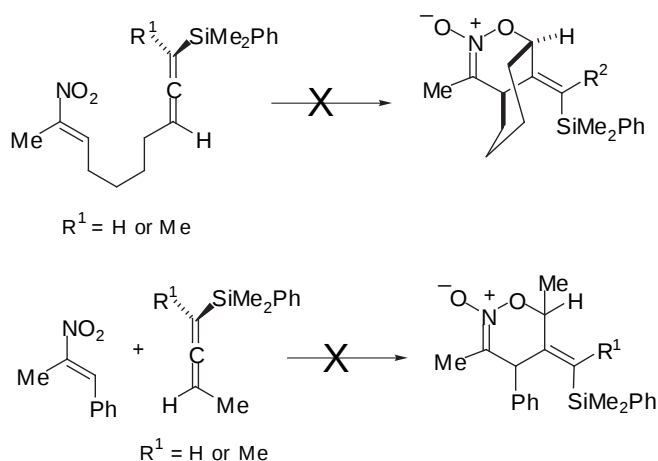
To evaluate the generality of this mode of [4+2] cycloaddition, we carried out the same reaction intermolecularly using allenylsilane (**14**), 2-methyl-2-nitrostyrene and SnCl_4 . The [4+2] cycloaddition was complete after 3 h at -78°C , but the resulting nitronate (**15**) could not be isolated. Accordingly, the crude reaction product was treated with 4-bromophenyl acrylate to produce the corresponding nitroso acetal as a mixture of three diastereomers (Scheme 10). Spectroscopic analysis confirmed the structure of the nitroso acetal (**16**).

Scheme 10



This result showed clearly that the regio- and stereochemical course of the reaction was independent of the tether. However our attempts to carry out this transformation with less substituted allenes either inter- or intramolecularly failed.

Scheme 11



The dramatic effect of substitution on the [4+2] cycloaddition between an allene and a nitroalkene clearly suggest that the reaction proceeds by development of positive charge on the γ -carbon of allenylsilane and that the silicon does not function as an effective activator of the allenyl unit for cycloaddition. Despite the failure of the allenylsilane unit to function as expected, the bicyclic nitronates (and nitroso acetals derived therefrom) are intriguing structures that have great potential for construction of highly functionalized seven-membered rings. Further studies on the application of the novel transformation are will be reported in due course.

ACKNOWLEDGEMENT

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14. The crystallographic coordinates of **13** have been deposited with the Cambridge Crystallographic Data Centre, deposition number 184380.

15. For a discussion of electrophilic additions to substituted allenes see ref. 9 pp. 61-76.
16. Although the stereochemical course of electrophilic substitution of allenylsilanes has been established as strongly anti-S_E2' (ref. 12), this reaction is not mechanistically related as the central carbon is being attacked. Indeed, electrophilic attack at this carbon generally occurs *syn* to the larger allenic substituent (c.f. ref. 15).