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INTRAMOLECULAR 4+3 CYCLOADDITIONS. VINYLTHIONIUM IONS FROM ALLYLIC ALCOHOLS

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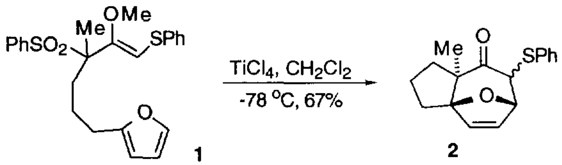
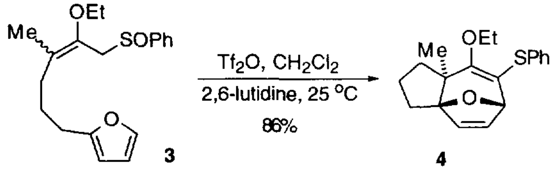
Summary: Aldehyde **9** can be prepared from ethyl pyruvate in several steps. Treatment of **1** with various diene-containing Grignard reagents results in the formation of the corresponding allylic alcohol in good yield. Exposure of these alcohols to triflic anhydride results in the formation of 4+3 cycloadducts in good to excellent yields. Furan and simple butadiene trap the intermediate allylic cation efficiently in the formation of 5,7-fused ring systems. A tethered thiophene undergoes only intramolecular Friedal-Crafts alkylation.

The intramolecular 4+3 cycloaddition reaction is a process with a great deal of potential for the synthesis of a variety of complex carbocycles.[1,2] As part of a long-term effort, we have been studying various aspects of the reaction from both a mechanistic and synthetic perspective.[3] Among some of the methodology we have developed, the use of heteroatom-stabilized allylic cations has been of particular interest.[3i] We have shown that vinylthionium ions as generated from either allylic sulfones (Equation 1) or allylic sulfoxides (Equation 2) participate effectively in the intramolecular 4+3 cycloaddition reaction. While both of these reactions are still under study in our laboratories, we uncovered some problems in both processes which prompted us to explore other possibilities for the generation of vinylthionium ion intermediates. Our initial attempts to use appropriately substituted allylic alcohols in this endeavor are the subject of this report.



1 2

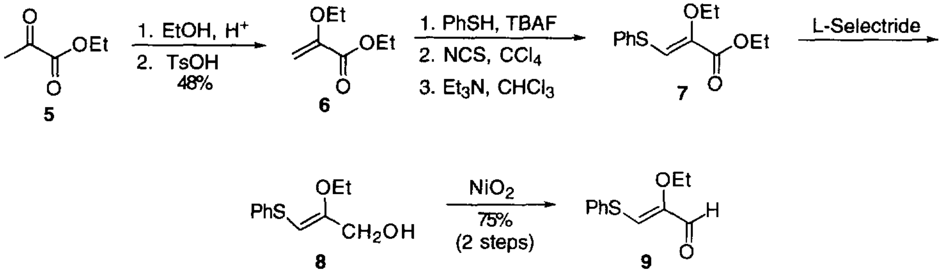
Equation 1



3 4

Equation 2

There are a number of known methods for the generation of vinylthionium ions and certainly many others possible.[4] It is apparently the case that simple allylic alcohols have not been used for the generation of these species in the development of new synthetic methodology for carbon-carbon bond formation.[5] We thus set out to pursue this approach. Our initial target became aldehyde **9**. The synthesis is shown in Scheme 1. Borrowing from methodology developed by Schmidt,[6] we treated ethyl pyruvate with acidic ethanol to obtain the corresponding ketal



Scheme 1

which was subsequently cracked under acidic conditions to give ethyl 2-ethoxyacrylate **6** in 48% overall yield. Conjugate addition of thiophenoxide, followed by α-chlorination and dehydrochlorination gave the ester **7** in 59% yield from **6**. The ester **7** was formed completely stereoselectively. The conversion of ester **7** to aldehyde **9** was not without some difficulty. Attempts to reduce ester **7** directly to **9** or to the corresponding alcohol **8** with aluminum hydride reagents were not successful. For example, treatment of **7** with REDAL led to 3-phenylthiopropan-1-ol in 53% yield. Eventually we found that L-Selectride worked quite nicely to reduce **7** to the corresponding alcohol **8**. Oxidation of the alcohol to **9** was also problematic. The use of PCC or PDC gave the aldehyde in 8% yield at best. Manganese dioxide gave the desired product in 25% yield and tetrapropylammonium perruthenate gave the aldehyde in 37% yield. We eventually found that nickel peroxide worked quite well for this oxidation and through its employment aldehyde **9** was reproducibly prepared from ester **7** in 60-75% yield.[7] The stereochemistry of **9** and hence **7** was established by an nOe study which which demonstrated an enhancement between the aldehyde and alkenyl hydrogens in **9**.

With **9** in hand we set out to synthesize cycloaddition substrates. Reaction of **9** with Grignard reagents worked well for this purpose. The results are shown in Table 1. A NOESY spectrum of **12** showed an enhancement between the carbinol methine hydrogen and the olefinic hydrogen , confirming that no isomerization has taken place during the addition process.

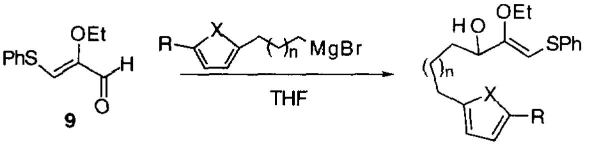
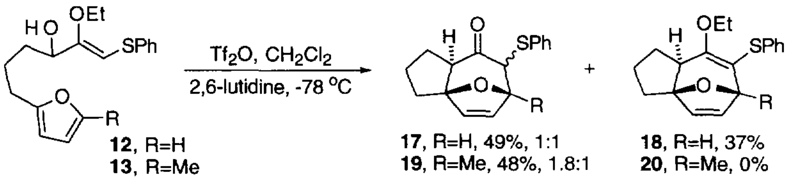


Table 1. Synthesis of Cycloaddition Substrates

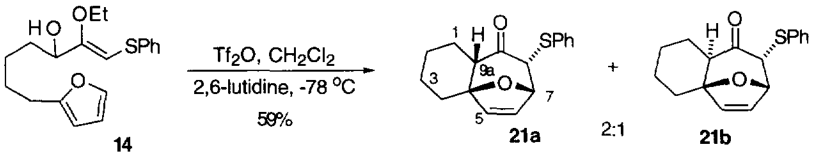
Entry	X	R	n	Yield (%)	Product
1	O	H	1	83	**12**
2	O	Me	1	90	**13**
3	O	H	2	83	**14**
4	H_2	H	1	54	**15**
5	S	H	1	77	**16**

Having prepared the requisite cyclization substrates we set out to conduct cyclization studies. Guided by precedent we chose to use triflic anhydride as the reagent to effect cation formation.[8] Treatment of a solution of **12** in dichloromethane with triflic anhydride at -78 °C resulted in the formation of cycloadducts **17** and **18** in 49% and 37% yields, respectively. While the ratio of ketone to enol ether could be varied slightly by changing work-up conditions, we have not been able to develop reaction condition in which either one or the other is exclusively or largely favored. The stereochemistry of **18** was unequivocally established by single crystal X-ray analysis.[9] The



Equation 3

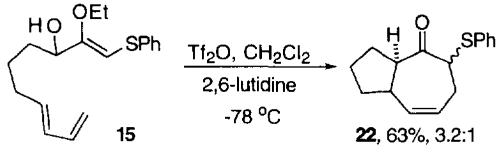
stereochemistry of **17** was assigned based on this result and other precedent.[3] Proton NMR analysis of this mixture suggested that the epimers were present were isomeric at C-7 and not at the ring juncture. Similarly, **13** cyclized to give a 48% yield of **19** as a 1.8:1 mixture of epimers. The fact that only ketonic products were obtained in this case is interesting but the reason for this is not yet clear. In addition, the precipitous drop in yield relative to **12** indicates the dramatic substituent effects which are possible in 4+3 cycloaddition reactions and suggests that caution must be used in extrapolating the success on a given reaction based on the success of even a structurally closely related substrate.



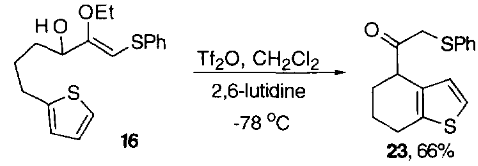
Equation 4

Similar treatment of **14** with Tf_2O gave a mixture of cycloadducts in 59% yield. The effect of adding an additional methylene group to the tether is substantial. Interestingly, only ketonic products were isolated in this case. The stereochemistry of the cycloadducts was assigned based on a NOESY spectrum of a mixture of cycloadducts. The major isomer **21a** showed a cross peak between the hydrogens assigned to C-9a and C-7, suggesting a syn relationship between these to hydrogens. Such an nOe was not observed in the minor isomer **21b**. Further, the C-9a hydrogen in **21b** showed a nOe with the corresponding olefinic hydrogen at C-5.

The diene **15** could likewise be cyclized to give 4+3 cycloadducts in 63% yield in a ratio of 3.2:1. The origin of the stereoisomerism in this case has not yet been ascertained. The lower yield relative to **12** is likely in response to the decrease nucleophilicity of the butadiene, s-cis/s-trans equilibrium, and/or the formation of side products not accessible to **12**.



Equation 5



Equation 6

Finally, despite precedent which suggested that a thiophene would not work as a diene in a 4+3 cycloaddition, we treated **16** with Tf_2O.[10] Interestingly, we obtained only the Friedel-Crafts alkylation product **23** in 66% yield. This is synthetically interesting as well: the allylic alcohol is essentially serving as as enolonium ion equivalent in this reaction.[11]

In summary, we have demonstrated that allylic alcohols can serve as precursors for vinylthionium ions which are good dienophiles in 4+3 cycloadditions. Further studies of this methodology and the use of such vinylthionium ions in other carbon-carbon bond forming processes are in progress and will be reported in due course.[12]

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9. MW=300.41; Space Group: $P2_1/c$; a = 12.064(2)A, b = 9.533(2)A, c = 14.872(3)Å, β = 108.72(2)^o; V = 1619.5(5)Å^3; Z = 4; Dcalc = 1.232; Radiation = CuKα (l = 1.54056)Å; μ = 1.74 mm^{-1}; F(000) = 642.92; Temperature = 23 ± 1^o; Final R = 0.035 for 2093 reflections with $I>2\sigma(I)$.
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12. All yields are for compounds after chromatographic purification. All new compounds have been characterized by ^1H and ^{13}C NMR, IR and combustion analysis.

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