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Acid-Promoted Prins Cyclizations of Enol Ethers To Form Tetrahydropyrans

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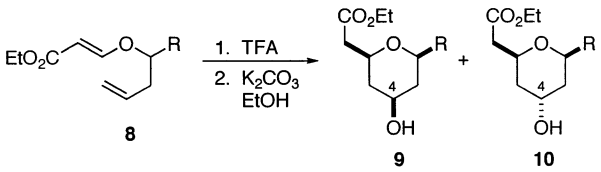
ABSTRACT



8 **9** **10**

Trifluoroacetic acid efficiently catalyzes Prins cyclizations of enol ethers 8 to provide tetrahydropyrans 9 and 10. These tetrahydropyrans are isolated with combined yields of 42–85% and stereoselectivities at C_4 ranging from 95:5 to 50:50 depending on the nature of the substituent R. Unique byproducts of these cyclizations that reveal the presence of underlying equilibria have been isolated and identified.

Prins cyclizations of oxocarbenium ions bearing an appended olefin represent a versatile method for the preparation of tetrahydropyrans.[1] These reactive oxocarbenium ions have been generated in a variety of ways. The best studied method involves acid-promoted reaction of homoallylic alcohols with aldehydes.[2] Ionization of acetals[3] and α-acetoxy ethers[4,5] and other related methods have also been studied.[6,7] Less studied is the generation of such oxocarbenium ions simply by protonation of enol ethers derived from homoallylic alcohols.[8] This paper describes observations that extend the scope and limitations of this route to tetrahydropyrans and reveal reaction pathways heretofore not reported for Prins cyclization reactions.

As a prelude to a target-oriented synthesis, we had reason to examine the reaction of acetal **1** with trifluoroacetic acid. This reaction gave tetrahydropyrans **2** (31−44%) and **3** (40−47%) after basic hydrolysis of presumed intermediate trifluoroacetates (Scheme 1). Whereas tetrahydropyran **2** had

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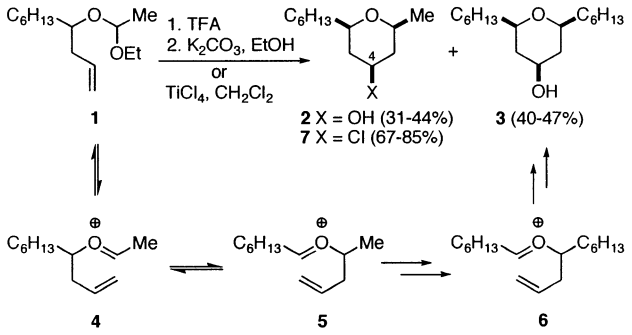
Scheme 1. Influence of Acid Promoter on Prins Cyclizations



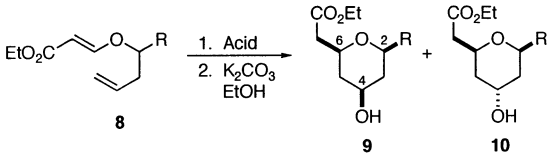
been expected, the appearance of **3** was a small surprise. We imagine that this product was derived from 1-decen-4-ol (from ionization of **1**) and heptanal or an appropriate derivative thereof (for example **5**), as illustrated in Scheme 1. This exchange process has been observed in several laboratories, and it is clear that the sigmatropic rearrangement (**4** → **5**) underlies several cyclization reactions of this type.[9,10] Nonetheless, this result underscores a limitation of the acetal route to 4-hydroxytetrahydropyran-1-ols. We also note that treatment of **1** with titanium tetrachloride in dichloromethane gave **7** along with its C_4 epimer in a 10:1 ratio (67−85%) in accord with literature precedent.[11] This indicates that the cyclization promoter also effects whether exchange reactions complicate this process.

Based on the results shown in Scheme 1, we decided to investigate a process that would lead to site selective generation of an oxocarbenium ion. It was reasoned that an enol ether might serve as an oxocarbenium ion precursor, and indeed, we were able to find precedence for this idea in the work of Nussbaumer and Frater.[8] Thus, we set out to investigate the scope of this little explored variation of the Prins cyclization route to tetrahydropyrans.

Some results are documented in Table 1 and Figure 1. Enol ethers of type **8** were prepared in 53−97% yield by treating the corresponding homoallylic alcohols with ethyl propiolate and triethylamine in Et_2O.[12] Exposure of these cyclization substrates to acid promoters gave results documented in Table 1 and Figure 1.

The results shown in entry 1 are similar to those reported by Nussbaumer and Frater. Thus, treatment of a 0.1 M dichloromethane solution of **8a** with 10 equiv of trifluoroacetic acid (TFA) at room temperature for 40 min gave a 76% isolated yield of pure **9a**, after ester ethanolysis under basic conditions. The epimeric alcohol **10a** was also isolated

Table 1. Acid-Promoted Cyclization of Enol Ethers



entry	substrate	R	acid[a]	time (h)	yield of **9** + **10** (%)	**9**/**10**
1	**8a**	*n*-C_6H_{13}	TFA	0.75	85[b]	91:9
2	**8a**	*n*-C_6H_{13}	HCO_2H[c]	2.25	12[b]	
3	**8b**	Ph	TFA	2.0	77	95:5
4	**8c**	CH_2OBn	TFA	5.25	58[b]	50:50
5	**8d**	$CH_2OTBDPS$	TFA	3.5	66[b]	57:43
6	**8e**	CH_2CH_2Bn	TFA	1.75	78	91:9
7	**8f**	$CH{=}CH_2$	TFA[c]	1.0	72[b]	91:9
8	**8g**	-≡-TMS	TFA	5.0	42[b]	80:20

[a] Unless otherwise noted, reactions were conducted as described in text for entry 1. [b] See text and Figure 1 for other products. [c] Acid was the solvent (0.25 M).

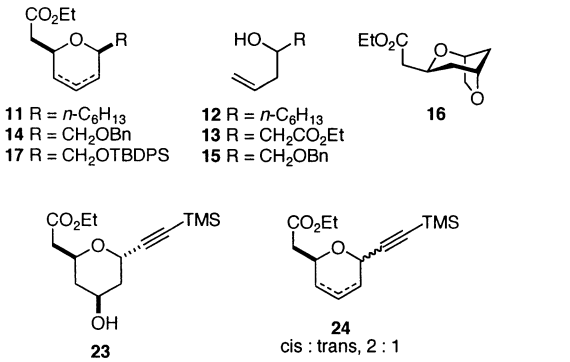


Figure 1. Byproducts of acid-promoted Prins cyclizations described in Table 1.

from this mixture, and it was determined that the ratio of **9a**:**10a** was approximately 10:1.[13] A mixture of dihydropyrans **11** was also isolated in 10−12% yield.[13,14]

The results shown in entry 2 underscore the influence of the cyclization promoter on the course of the reaction. Thus, treatment of **8a** with formic acid gave **9a** in only 12% yield along with starting material (15%), homoallylic alcohols **12** (10%) and **13** (17%), and crossover product **3** (24%). This illustrates that formal hydrolysis (**3** and **12**) and sigmatropic rearrangements (**13**) can complicate cyclization reactions with enol ether substrates of type **8**.

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(12) Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572.
(13) Relative stereochemistry of products was assigned based on 1D- and 2D-^{1}H NMR experiments, described in the Supporting Information.
(14) The isomeric relationships of dihydropyrans **11**, **14**, and **17** were established by catalytic hydrogenation of the mixtures to corresponding single tetrahydropyrans. Hydrogenation of **24** gave two tetrahydropyrans.

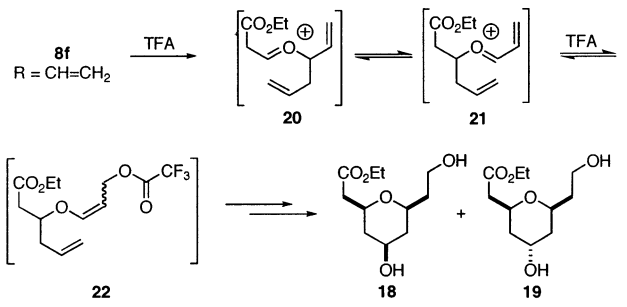
The behavior of **8b** with trifluoroacetic acid (entry 3) reveals that this process can be extended to the synthesis of 2-aryltetrahydropyrans. The behavior of **8c** upon reaction with TFA was more interesting (entry 4). This reaction gave a 1:1 mixture of tetrahydropyrans **9c** and **10c** (55−58%), dihydropyrans **14** (10−13%), alcohols **13** (trace) and **15** (11%), 2,6-dioxabicyclo[3.2.1]octane **16** (12%), and benzyl alcohol (trace).[13,14] Two aspects of this reaction are interesting. First, stereochemical control at C_4 of the tetrahydropyran undergoes considerable erosion relative to entries 1 and 3. Second, bicyclic ether **16** appears as a heretofore unobserved Prins cyclization product. This product is notable because of the trans relationship between the C_2 and C_6 substituents of the pyran substructure.[15]

Whereas the exact sequence of events leading to **16** has not yet been determined, it was hoped that replacement of the benzyl group with a protecting group less prone to acid-promoted cleavage would eliminate this competing process. Thus, substrate **8d** was prepared and treated with TFA (entry 5). This reaction provided a 4:3 mixture of tetrahydropyrans **9d** and **10d** (66%), dihydropyrans **17** (13%), and bicyclic ether **16** (trace).[13,14] Thus, changing the protecting group impeded dioxabicyclo[3.2.1]octane formation but did not correct the stereochemical erosion at C_4.

Enol ether **8e** (entry 6), the methylene homologue of **8c**, gave only the expected cyclization products **9e** and **10e** in 91:9 ratio (80%).[13] This result confirms that the side chain oxygens in **8c** and **8d** play a role in the stereochemical erosion at C_4 observed with these substrates.

We next examined hybridization changes in the incipient C_2 side chain. Substrate **8f** (sp^2-hybridized side chain) behaved normally when the reaction was run in neat trifluoroacetic acid (entry 7) to give a separable mixture of **9f** and **10f** in a 91:9 ratio and greater than 70% yield.[13] When the concentration of trifluoroacetic acid was reduced, however, diols **18** and **19** (2:1, respectively) appeared as interesting minor products in up to 13% yield at the expense of **9f** and **10f**.[16] We suggest that these compounds are formed as illustrated in Scheme 2.

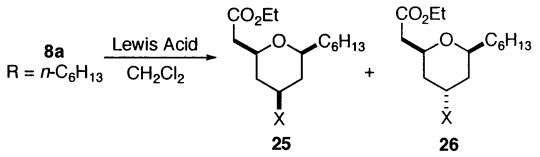
Scheme 2. Formation of Diols **18** and **19** during TFA-Promoted Prins Cyclization of Enol Ether **8f**



Substrate **8g** (sp-hybridized side chain) gave the expected products **9g** (33%) and **10g** (9%) along with homoallylic alcohol **13** (4%), trans-2,6-disubstituted pyran **23** (27%) and a mixture of cis-2,6- and trans-2,6-disubstituted dihydropyrans **24** in 9% combined yield (cis/trans = 2:1).[13,14] The reduced 2,6-selectivity with **8g**, relative to all other substrates in Table 1, can be attributed to reduced steric requirements for an alkynyl group in the presumed chairlike transition state believed to dominate the Prins cyclization route to tetrahydropyrans.[9]

We have also extended the Nussbaumer−Frater version of the Prins cyclization to other acid promoters. Treatment of **8a** with titanium tetrachloride in dichloromethane gave **25** and **26** (X = Cl) in 63% yield as a 20:1 mixture, respectively (Table 2).[13] Similar treatment of **8a** with titanium tetrabromide or tin tetrabromide gave **25** and **26** (X = Br) with slightly lower diastrereoselectivity at C_4.[13] The slow reaction rates (2−3 days) for titanium tetrachloride and tin tetrabromide mediated reactions suggest that an alternative mode of activation, such as Lewis acid complexation of the vinylogous carbonate carbonyl group, may be operating.

Table 2. $TiCl_4$-, $TiBr_4$-, and $SnBr_4$-Promoted Prins Cyclizations



entry	acid	*T* (°C)	time	X	yield of **25** + **26** (%)	**25**/**26**
1	$TiCl_4$	rt	3 d	Cl	63	20:1
2	$TiBr_4$	0	2 h	Br	64	6:1
3	$SnBr_4$	rt	2.5 d	Br	69	5:1

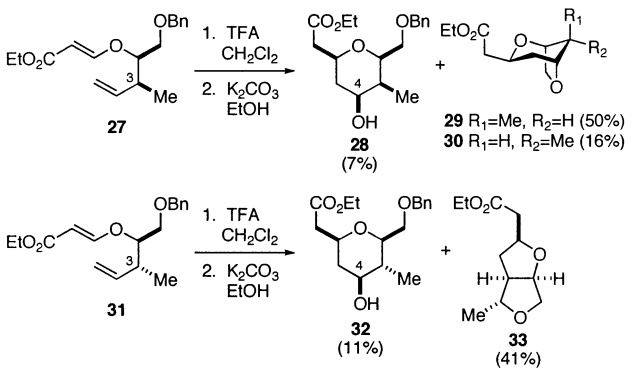
Finally, we have observed that a simple methyl substituent at C_3 in substrates related to **8c** can have a dramatic effect on the course of the reaction (Scheme 3). For example, treatment of **27** with TFA in dichloromethane provided the expected tetrahydropyran **28** in only 7% yield.[13] The major product was dioxabicyclo[3.2.1]octane **29** (50%) accompanied by its C_3 epimer **30** (16%).[13] Reaction of the C_3 epimeric substrate **31** with TFA gave a largely different set of products. The expected tetrahydropyran **32** was once again a minor product isolated in 11% yield along with 4% of the corresponding C_4 epimer.[13,17] The major product was now dioxabicyclo[3.3.0]octane **33** (41%).[13] Bicyclic diethers **29** (6%) and **30** (4%) were also obtained. We suspect that **30** was the major bicyclo[3.2.1]octane produced from **31**, while most of **29** produced in this reaction arises from the 10% contamination of **31** with **27**.[18]

(15) For closest analogy to this, see Speckamp and Hiemstra. For cases with CH_2OBn where no participation was observed, see: Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426.

(16) The structure of **18** was correlated with that of **9f** by hydroboration (9-BBN)/oxidation of the latter.

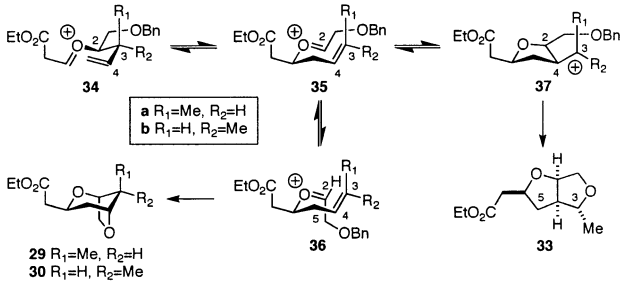
(17) We note that only a trace of **32** (less than 1%) was detected in the cyclization of **27**.

Scheme 3. Prins Cyclizations of C_3-Methyl-Substituted Enol Ethers **27** and **31**



Although we can only speculate about the divergent behavior of **27** and **31**, a working hypothesis is presented in Scheme 4. We imagine that **27** and **31** are protonated to

Scheme 4. Possible Mechanistic Pathway for the Formation of Bicycles **29**, **30**, and **33**



afford oxocarbenium ions **34a** and **34b**, respectively. Cyclization of these compounds to the observed tetrahydropyrans appears to take place via the expected chairlike conformation without erosion of stereochemistry across C_2 and C_3. Sigmatropic rearrangement of **34a** and **34b** via a chairlike conformation would provide oxocarbenium ions **35a** and **35b**, respectively. Isomerization of oxocarbenium ion geometry via addition−elimination of nucleophiles present in the reaction mixture would provide oxocarbenium ions **36a** and **36b**, respectively. Cyclization of **36a** and **36b** via a chairlike transition states would ultimately provide dioxabicyclo[3.2.1]-octanes **29** and **30**, respectively, as the major stereoisomers. We note that this hypothesis explains the apparent switch in the diastereomeric C_2-C_3 relationship observed in this pair of products. Furthermore, sigmatropic rearrangement of **34a** through a boatlike conformation would afford **35b**, providing a path from **34a** to the minor product **30**.[9] On the other hand, cyclization of **35b** to secondary carbocation **37b** followed by trapping of the cation by the benzylic oxygen would provide **33**. It is possible that the cyclization rate of **37a** is slower than the cyclization rate of **37b** because of an unfavorable steric interaction resulting from endo placement of the C_6-methyl group in the cyclization of **37a**. This could explain why **27** provides dioxabicyclo[3.2.1]octane **29** as the major product, while **31** provides largely dioxabicyclo[3.3.0]-octane **33**. Although further studies are needed to see which aspects of Scheme 4 have merit, this hypothesis provides a mechanistic framework for thinking about these reactions and designing mechanistic experiments.

In summary, this research further defines the scope and limitations of the Nussbaumer−Frater version of the Prins cyclization route to tetrahydropyrans. Several major reactions that have not been reported by groups that have studied variations of the Prins cyclization are also described.

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Supporting Information Available: Representative experimental procedures for Prins cyclizations of enol ethers and spectroscopic data for the resulting products are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Vinylogous carbonate was prepared as described above from the appropriate homoallylic alcohol, which was prepared by crotylation of 2-benzyloxyacetaldehyde by the $CrCl_2-NiCl_2$ method: Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. **31** prepared in this manner was contaminated with 10% of **27** (by ^1H NMR).