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Solvolysis of a Tetrahydropyranyl Mesylate: Mechanistic Implications for the Prins Cyclization, 2-Oxonia-Cope Rearrangement, and Grob Fragmentation

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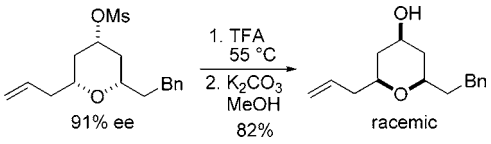
ABSTRACT



A solvolysis reaction is used to demonstrate that a tetrahydropyranyl cation is a common intermediate for Prins cyclizations, 2-oxonia-Cope rearrangements, and Grob fragmentations of tetrahydropyran rings.

The Prins cyclization and the 2-oxonia-Cope rearrangement are highly stereoselective carbon−carbon bond forming reactions that have received considerable attention from organic chemists.[1−3] Both transformations are initiated by an oxocarbenium ion and a tethered alkene and thus are mechanistically related. Not surprisingly, the two processes are often competing pathways.[4] Recently, we reported our investigations into the relative rates of 2-oxonia-Cope rearrangements and Prins cyclization reactions.[5] The mechanistic model set forth in that document was inspired by calculations from Alder suggesting a common cationic intermediate for both transformations.[6]

Figure 1 outlines the proposed mechanistic pathways.[5] In this model, tetrahydropyranyl cation **3** serves as a branch point in a 2-oxonia-Cope rearrangement (**2** to **4**) and Prins cyclization reaction (**2** to **5**).[7] Alder suggested that tetrahydropyranyl cation **3** has increased stability due to extensive delocalization. The optimal geometry for this delocalization

(1) For reviews on the Prins cyclization see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *52*, 505−555. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (c) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.

(2) For recent work on the Prins cyclization see: (a) Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem Soc.* **2005**, *127*, 16044−16045. (b) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663. (c) Yadav, K. V.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652−8653. (d) Hart, D. J.; Bennet, C. E. *Org. Lett.* **2003**, *5*, 1499−1502. (e) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Huges, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429−2432. (f) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, 1979−1982.

(3) (a) For recent work on the 2-oxonia-Cope see: Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. I. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (c) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (d) Loh, T.-P.; Ken Lee, C.-L.; Tan, K.-T. *Org. Lett.* **2002**, *4*, 2985−2987. (e) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *Org. Lett.* **2002**, *4*, 2389−2391. (f) Lee, C.-L. K.; Lee, C.-H. A.; Tan, K.-T.; Loh, T.-P. *Org. Lett.* **2004**, *6*, 1281−1283.

(4) (a) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra. H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129−7140. (b) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955−959. (c) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818. (d) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580. (e) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407−3410. (f) Hart, D. J.; Bennet, C. E. *Org. Lett.* **2003**, *5*, 1499−1502.

(5) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939−9945.

(6) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960−4961.

(7) For trapping experiments of proposed charged intermediates in Prins cyclizations and 2-oxonia-Cope rearrangements see: (a) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, *29*, 3727−3729. (b) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818.

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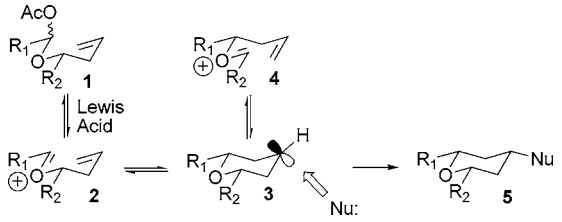


Figure 1. Stepwise Prins cyclization reaction and 2-oxonia-Cope rearrangement.

places the hydrogen in the pseudoaxial position, which directs nucleophilic attack along an equatorial trajectory. The extensive delocalization therefore provides rationale for the 2,4,6-cis stereoselectivity commonly observed for Prins cyclization reactions.[8,9]

The energy diagram in Figure 2 further details the calculations reported by Alder.[6] Tetrahydropyranyl cation **6** was calculated to have a ground state energy 13.4 kJ/mol higher than that of oxocarbenium ion **7**. In addition, the

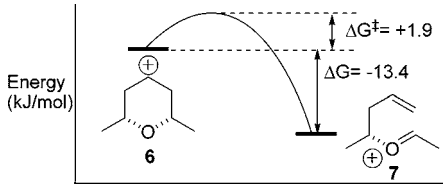


Figure 2. Energetics of a tetrahydropyranyl cation.

barrier for ring-opening was calculated to be only 1.9 kJ/mol. On the basis of these calculations, we surmised that generation of a tetrahydropyranyl cation should rapidly lead to an oxocarbenium ion. Such a ring-opening process would represent the first known Grob fragmentation of a tetrahydropyran ring, the reverse of a Prins cyclization. In this way, the delocalized tetrahydropyranyl cation may serve not only as an intermediate for Prins cyclizations and 2-oxonia-Cope rearrangements, but also for Grob fragmentations of tetrahydropyran rings. In this Letter, we report a solvolysis reaction linking all three processes to the delocalized tetrahydropyranyl cation intermediate proposed by Alder.

Figure 3 outlines a test to identify a Grob fragmentation pathway for a tetrahydropyran ring. A solvolysis reaction of appropriately substituted tetrahydropyran **8** should generate tetrahydropyranyl cation **9**. Cation **9** could then undergo nucleophilic attack to produce optically active tetrahydropyran **10**. In contrast, tetrahydropyranyl cation **9** may

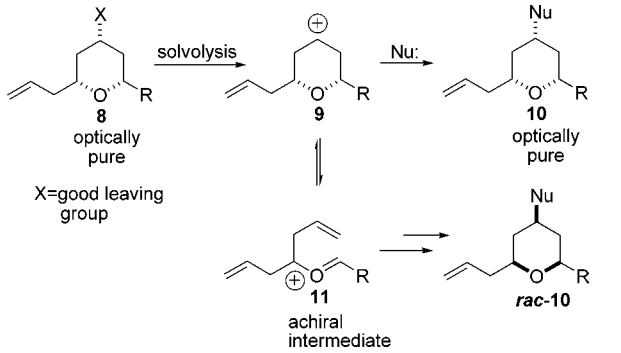
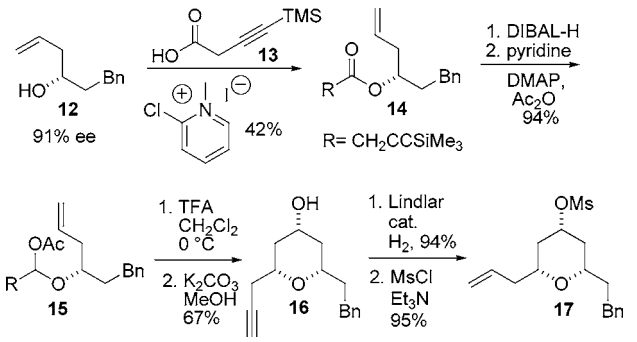


Figure 3. Racemization as an indicator for Grob fragmentation.

undergo a fast ring-opening process to generate achiral oxocarbenium **11**. Prins cyclization of achiral oxocarbenium ion **11** would then necessarily lead to racemic **10**. Therefore, racemization of tetrahydropyran **10** can be used as an indicator for a Grob fragmentation pathway.

With the racemization test in mind, we turned our attention to the synthesis of optically active tetrahydropyranyl mesylate **17** (Scheme 1). Ester **14** was prepared in 42% yield from

Scheme 1. Synthesis of Mesylate **17**



optically active alcohol **12**[10] and carboxylic acid **13**.[11] Reductive acetylation conditions developed in our laboratory smoothly converted ester **14** to acetoxy ether **15** as a 1:1 mixture of diastereomers.[12] Prins cyclization of **15** followed by methanolysis delivered tetrahydropyran **16** in 67% yield over 2 steps.[13] Reduction and mesylation completed the synthesis of tetrahydropyran **17**.

Trifluoroacetolysis[14] of optically active tetrahydropyran **17** followed by methanolysis provided racemic tetrahydropyran **18** as a single diastereomer in 82% yield (Scheme 2).[15]

(8) Under standard Prins cyclization conditions, nucleophilic trapping (**3** to **5**) is not reversible.

(9) For axial-selective Prins cyclizations, see: (a) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905. (b) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115−7128. (c) Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493−1501.

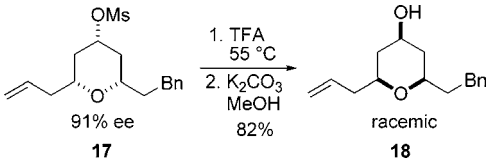
(10) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.

(11) Davies, H. M. L.; Boebel, T. A. *Tetrahedron Lett.* **2000**, *41*, 8189−8192.

(12) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.

(13) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Huges, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429−2432.

Scheme 2. Trifluoroacetolysis of Mesylate **17**



Racemization of tetrahydropyran **18** indicates that ring-opening is faster than nucleophilic attack by trifluoroacetate. This result provides the first evidence of a Grob fragmentation pathway for tetrahydropyran rings. One question remaining was whether this was a concerted or a stepwise process. Figure 3 illustrates a Grob fragmentation of **8** occurring by way of discrete carbocation intermediate **9** (i.e., asynchronous Grob fragmentatation). Is it possible that solvolysis of **8** in fact leads directly to achiral oxocarbenium ion **11** via a synchronous Grob fragmentation?

In his classic studies, Grob distinguished between asynchronous and synchronous fragmentation reactions by comparing rates of solvolysis with carbon analogues (Figure 4).[16]

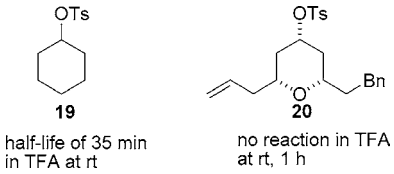


Figure 4. Trifluoroacetolysis of carbon analogue **19** and tetrahydropyran **20**.

Cyclohexyltosylate **19** has been shown to have a half-life of 35 min in trifluoroacetic acid at room temperature.[17] In contrast, subjecting tetrahydropyran **20** to similar conditions resulted in no reaction. In a synchronous fragmentation reaction, the heteroatom substituted compound should undergo solvolysis more rapidly or at a similar rate to the carbon analogue due to favorable n_O to σ^*_{C-C} interactions. In an asynchronous fragmentation, the heteroatom inductively destabilizes the C4 cationic intermediate, thus slowing the rate of solvolysis relative to the carbon analogue. Our results are consistent with an asynchronous fragmentation, in which the inductive effect of the heteroatom decreases the reactivity of tetrahydropyran **20** toward acid-catalyzed solvolysis.

With the results from the solvolysis reactions in hand, a mechanistic scheme can be constructed in which the Prins cyclization, 2-oxonia-Cope rearrangement, and Grob fragmentation all proceed through one common intermediate (Figure 5). Trifluoroacetolysis of mesylate **17** leads to

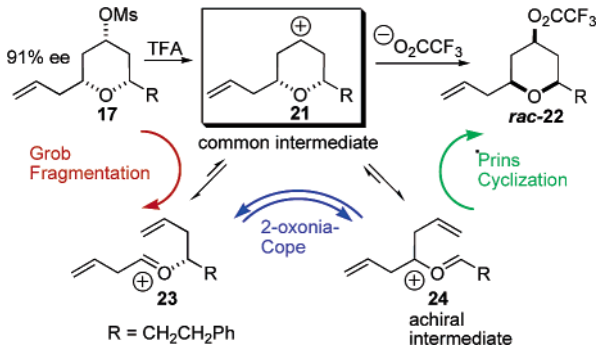
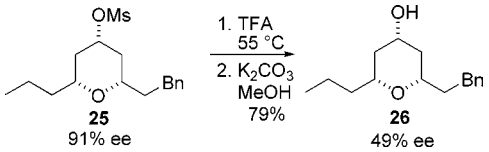


Figure 5. Tetrahydropyranyl cation **21** as a common intermediate for a Prins cyclization, a 2-oxonia-Cope rearrangement, and a Grob fragmentation.

tetrahydropyranyl cation **21**. Tetrahydropyranyl cation **21** can then ring-open, presumably, with equal probability to either oxocarbenium ion **23** or achiral oxocarbenium ion **24**. Tetrahydropyranyl cation **21** therefore is an intermediate for a Grob fragmentation of tetrahydropyran **17**. In addition, oxocarbenium ions **23** and **24** can interconvert by undergoing a ring-closure process followed by a ring-opening. In this way, tetrahydropyranyl cation **21** also serves as an intermediate for a 2-oxonia-Cope rearrangement. Furthermore, the asynchronous nature of the Grob fragmentation implies that the reverse reaction, a Prins cyclization, is also asynchronous. Thus, oxocarbenium ions **23** and **24** lead to **22** by way of the same tetrahydropyranyl cation intermediate **21**. Interestingly, although the Prins cyclization proceeds through a cationic intermediate, only one isomer is observed at C4. This result is consistent with Alder's description of extensive delocalization for tetrahydropyranyl cations such as **21**.[5,6]

Ring-opening of tetrahydropyranyl cation **21** to achiral oxocarbenium **24** was assumed to be the only pathway for racemization. To test the validity of this assumption, saturated tetrahydropyran **25** was prepared. In this case, an achiral intermediate is not available by a simple Grob fragmentation. Surprisingly, trifluoroacetolysis of saturated tetrahydropyran **25** followed by methanolysis led to alcohol **26** in only 49% ee (Scheme 3). The loss in optical activity for **26** indicates the presence of a second racemization pathway that is independent of achiral intermediate **24**. The erosion in

Scheme 3. Trifluoracetolysis of Mesylate **25**



(14) Trifluoroacetic acid has been shown to have an exceptional combination of high solvolytic power and low nucleophilicity. See the following and references therein: Nordlander, J. E.; Gruetzmacher, R. R.; Kelly, W. J.; Jindal, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 181−185.

(15) Nucleophilic attack by trifloroacetate is not reversible. Subjecting optically active tetrahydropyranyl trifluoroacetate to solvolysis conditions results in no reaction.

(16) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535−546.

(17) Lambert, J. B.; Putz, G. J. *J. Am. Chem. Soc.* **1973**, *95*, 6313−6319.

enantiomeric excess for this reaction may involve isomerization of an (*E*)-oxocarbenium ion to a (*Z*)-oxocarbenium ion followed by a 2-oxonia-Cope rearrangement.[18] Efforts to unravel this unusual racemization pathway are currently underway in our laboratory and will be reported in due course.

In conclusion, we have demonstrated a novel solvolysis reaction of a tetrahydropyranyl mesylate. The outcome of this solvolysis reaction correlates well with a mechanistic model in which a delocalized tetrahydropyranyl cation serves as an intermediate for Prins cyclizations, 2-oxonia-Cope rearrangements, and Grob fragmentations of tetrahydropyran rings. This knowledge should be useful for further development and application of these transformations.

(18) For similar racemization pathways in iminium ion cyclizations see: (a) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919−3930. (b) Castro, P.; Overman, L. E. *Tetrahedron Lett.* **1993**, *34*, 5243−5246.

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Supporting Information Available: Experimental procedures and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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