ORGANIC LETTERS

2002
Vol. 4, No. 4
577−580

Oxonia-Cope Rearrangement and Side-Chain Exchange in the Prins Cyclization

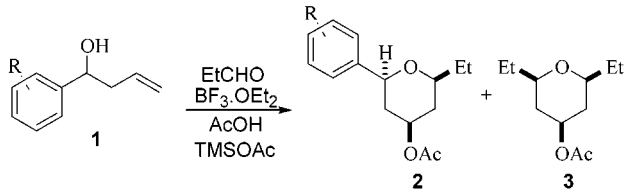
Stuart R. Crosby,[†] John R. Harding,[‡] Clare D. King,[‡] Gregory D. Parker,[†] and Christine L. Willis*,[†]

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K., and AstraZeneca UK Ltd., Mereside, Alderley Park, Macclesfield, SK10 4TG, U.K.

chris.willis@bristol.ac.uk

Received December 5, 2001

ABSTRACT



Evidence is presented here for the mechanism of the Prins cyclization of benzylic homoallylic alcohols, which shows that the outcome of the reaction is dependent upon the substituents on the aromatic ring. The presence of an electron-rich aromatic ring favors an oxonia-Cope rearrangement yielding a symmetrical tetrahydropyran as the major product formed via a side-chain exchange process. In contrast, with electron-deficient aromatic rings the expected 2,4,6-trisubstituted tetrahydropyran is formed.

In recent years, there has been widespread interest in the use of Prins cyclizations for the stereocontrolled synthesis of 2,4,6-trisubstituted tetrahydropyrans.[1] These reactions are believed to proceed via formation of an oxocarbenium ion (generated in situ either from reaction of a homoallylic alcohol with an aldehyde or from a homoallylic acetal) that undergoes an intramolecular cyclization, giving the tetrahydropyran with all three substituents located in an equatorial position. It has been suggested that cationic oxonia-Cope rearrangements may participate in Prins cyclisations and related reactions as illustrated in Figure 1.[2]

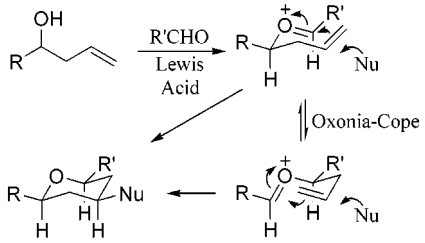


Figure 1. Oxonia-Cope rearrangement.

Most literature examples of the synthesis of tetrahydropyrans by such cyclizations have utilized homoallylic alcohols with aliphatic side chains as the starting material. At

[†] University of Bristol.
[‡] AstraZeneca UK Ltd.

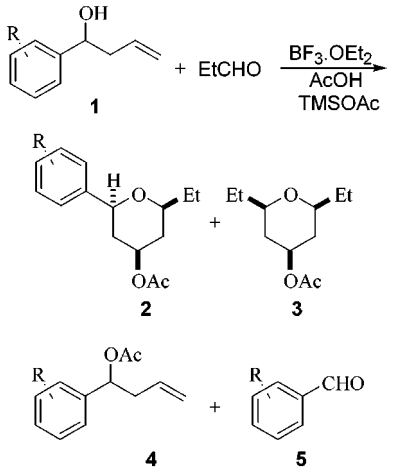
(1) For example: (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc*. **1999**, *121*, 1092. (b) Yang, J.; Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett*. **1999**, *40*, 1627. (c) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett*. **1998**, *39*, 7271. (d) Markó, I. E.; Chellé, F. *Tetrahedron Lett*. **1997**, *38*, 2895.

(2) Examples of such rearrangements include: (a) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem*. **2001**, *66*, 4679. (b) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 2, 3426. (c) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129. (d) Gasparski, C. M.; Herrington, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett*. **2000**, *41*, 9431. (e) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc*. **2001**, *123*, 2450. (f) Brown, M. J.; Harrison, T.; Herrington, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *J. Am. Chem. Soc*. **1991**, *113*, 5365.

10.1021/ol0102850 CCC: $22.00
Published on Web 01/30/2002

the start of our investigations, we proposed that if the homoallylic alcohol has a side chain with an electron-rich aromatic ring such as **1a** (Table 1), then it would be reasonable to expect an oxonia-Cope rearrangement to be favored through stabilization of the positive charge.[3]

Table 1. Reaction of Alcohols 1a−g with BF_3·OEt_2 (2 Equiv), AcOH (5 Equiv), and TMSOAc (4 Equiv) in C_6H_{12} at Room Temperature



Yields of products

entry	R =	**2** (%)	**3** (%)	**4** (%)	**5** (%)	**1** (%)
i	**1a**; 3,4-OCH_2O	20	21	26	17	
ii	**1b**; 4-OMe	15	21	21	18	
iii	**1c**; H	54	24		23	
iv	**1d**; 3-F	46	9		9	23
v	**1e**; 2-Cl	57				36
vi	**1f**; 4-NO_2[a]	36				43
vii	**1g**; 3,4,-diOAc	67				

[a] 7% of the 4-F analogue was isolated due to extended reaction time (16 h).

To test this hypothesis, homoallylic alcohol **1a** was prepared in 92% yield from commercially available piperonal and allylmagnesium bromide. Several methods have been reported for the introduction of oxygenated substituents at C-4 of tetrahydropyrans in Prins cyclizations with varying success.[4] In recent studies into the stereocontrolled synthesis of 4-hydroxy-2,5-disubstituted tetrahydropyrans, we have shown that hydrolysis of the esters formed from reaction of homoallylic acetals with either trifluoroacetic acid or with BF_3·OEt_2 in the presence of AcOH as the nucleophile and TMSOAc to act as a fluoride trap gave yields of between 50 and 70%.[5]

Thus, cyclization of homoallylic alcohol **1a** with propanal was investigated using BF_3·OEt_2 in the presence of AcOH and TMSOAc in cyclohexane at room temperature to give the expected tetrahydropyran **2a** as a single diastereomer but in only 20% yield (entry i, Table 1). Interestingly, three further products were isolated including the allylic acetate **4a** and the parent aldehyde **5a**, and of particular interest was another tetrahydropyran **3** formed in 21% yield. The plane of symmetry was clearly revealed in the ^{13}C NMR spectrum of **3**, which contained only seven signals. To the best of our knowledge, this is the first example of a Prins-type cyclization involving a homoallylic alcohol and aldehyde (with different side chains) to give a symmetrical 2,4,6-trisubstituted tetrahydropyran and must involve an allyl transfer process. Side-chain exchanges have been reported in other cyclizations. For example, a recent paper by Roush and Dilley[6] describes the preparation of 2,6-disubstituted dihydropyrans from allylsilanes, and Li and co-workers[7] detected symmetrical 2,4,6-thiacyclohexanes by GC/MS on treatment of homoallylic thiols with an aldehyde in the presence of indium trichloride.

To further investigate the effect that the nature of the aromatic ring has on the outcome of the Prins cyclizations, a series of substituted aromatic homoallylic alcohols **1b**−**g** was prepared in good yield by reaction of allyl iodide with the substituted benzaldehyde in the presence of indium powder in water.[8] Each homoallylic alcohol was treated with propanal in the presence of BF_3·OEt_2, AcOH, and TMSOAc at room temperature, and following workup, the products were purified by flash chromatography (Table 1). In accord with the results from cyclization of the 3,4-methylenedioxy derivative **1a**, the electron-rich anisaldehyde derived homoallylic alcohol **1b** gave rise to a greater proportion of the symmetrical product **3** than the trisubstituted heterocycle **2b** (entry ii, Table 1). In addition, it is interesting to note that the homoallylic acetate **4b** and the parent aldehyde **5b** were also isolated. Cyclization of homoallylic alcohols **1c** and **1d** (prepared from benzaldehyde and 3-fluorobenzaldehyde, respectively) gave the tetrahydropyrans **2c** and **2d**, respectively; in each case, the symmetrical compound **3** was only a minor product. In contrast, when homoallylic alcohols **1e**, **1f**, and **1g** (derived from 2-chlorobenzaldehyde, 4-nitrobenzaldehyde, and 3,4-diacetoxybenzaldehyde, respectively) were treated with propanal under the standard cyclization conditions, the only products isolated in each case were the expected tetrahydropyrans **2e**, **2f**, and **2g** along with recovered starting material.

Since homoallylic acetates are only detected as products in the cyclization studies with electron-rich aromatic rings (entries i and ii, Table 1), a stabilized carbocation intermedi-

(3) We are grateful to Professor S. D. Rychnovsky for sharing his fascinating results with us prior to publication in which he showed that the intermediate from an oxonia-Cope rearrangement may be trapped by reduction with Bu_3SnH: Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815.

(4) (a) Nishizawa, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett*. **1999**, *40*, 1153. (b) Zhang, W.-C.; Viswanathan, G. S.; Li, C.-J. *Chem. Commun*. **1999**, 291. (c) Zhang, W.-C.; Li, C.-J. *Tetrahedron* **2000**, *56*, 2403. (d) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett*. **1996**, *37*, 8679. (e) Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993. (f) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022.

(5) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun*. **2001**, 835.

(6) Roush, W. R.; Dilley, G. J. *Synlett*. **2001**, 955.

(7) Yang, X. F.; Mague, J. T.; Li, C.-J. *J. Org. Chem*. **2001**, *66*, 739.

(8) Chan, T. H.; Lee, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem*. **1994**, *72*, 1181.

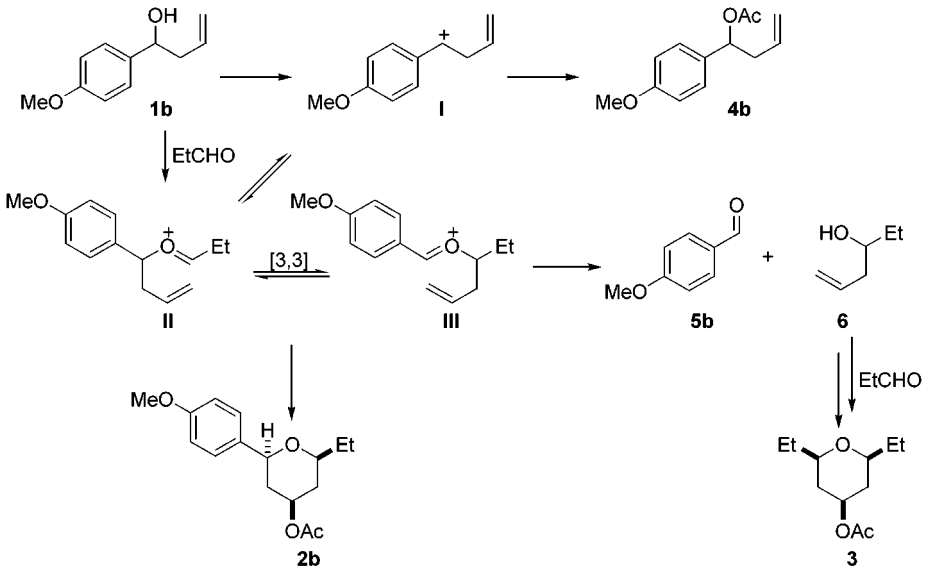
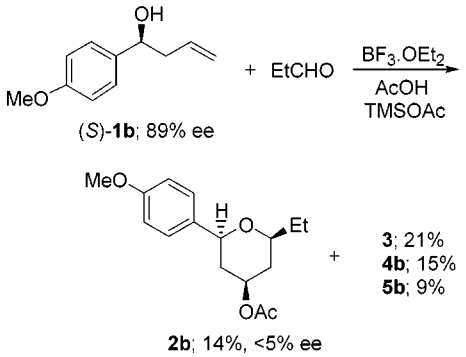


Figure 2. Proposed mechanism for formation of products **2b**, **3**, **4b**, and **5b** on treatment of **1b** with EtCHO, TMSOAc, and AcOH + BF_3·OEt_2.

ate **I** is implicated (Figure 2). To probe for such an intermediate, first homoallylic alcohols with either an electron-rich (R = 4-OMe) or electron-poor (R = 3-F) aromatic ring, **1b** and **1d**, respectively, were each simply treated with BF_3·OEt_2, AcOH, and TMSOAc in cyclohexane at room temperature (i.e., no propanal was added). In the case of the 4-methoxy substrate **1b**, the acetate **4b** was formed in quantitative yield, whereas the reaction with the 3-fluoro derivative **1d** was slower giving a 2:1 mixture of starting alcohol **1d** and acetate **4d**. These results are in accord with the proposal that the acetates **4a** and **4b** are formed via the stabilized carbocation intermediate **I**.

The mechanism of the reaction was further investigated using the enantioenriched homoallylic alcohol (*S*)-**1b**, which was prepared in good yield (77%) and 89% ee (as determined via analysis of the Moshers ester derivative) by a modification of the method of Brown and co-workers.[10] Reaction of (*S*)-**1b** with propanal, BF_3·OEt_2, AcOH, and TMSOAc gave the four expected products, which were readily separated by flash chromatography (Scheme 1). Homoallylic acetate **4b** was racemic in accord with the proposed mechanism involving a stabilized carbocation intermediate **I** (Figure 2). In addition, we found that the 2,4,6-trisubstituted tetrahydropyran **2b** had very low ee (<5%), as determined by chiral HPLC. This was rather unexpected as there are literature examples of Prins cyclizations in which the enantioenrichment in the parent alcohol is retained in the oxygen heterocycles produced.[2c,6] In this case, however, the initially produced oxocarbenium ion **II** may be formed either by attack of **I** by propanal or directly from alcohol **1b** by reaction with propanal and dehydration, thus accounting for the low ee of 2,4,6-trisubstituted tetrahydropyran **2b** (Figure 2).

Scheme 1. Cyclization of Enantioenriched Alcohol (*S*)-1b.



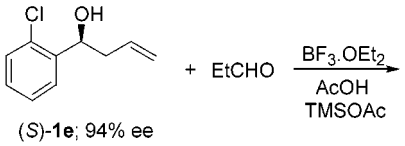
If, as expected, the oxonia-Cope rearrangement of **II** to **III** is favored in the case of an electron-rich aromatic side chain due to resonance stabilization of the positive charge, then the symmetrical tetrahydropyran **3** may be formed by the mechanism shown in Figure 2. Nucleophilic attack (by either water or acetate) on **III** would lead to the parent aldehyde **5** and the homoallylic alcohol **6** with an aliphatic side chain, hence effecting the necessary allyl transfer reaction for the synthesis of the symmetrical product. The symmetrical tetrahydropyran and aldehyde are produced in an approximately a 1:1 ratio, in accord with the proposed mechanism.

Next, we turned our attention to the cyclization of an enantioenriched homoallylic alcohol with an electron-deficient aromatic ring, and we selected the 2-chloro deriva-

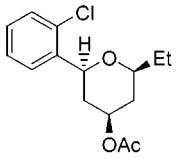
(9) Allyl-transfer reactions of homoallylic alcohols have been noted previously; see, for example: (a) Nokami, J.; Yoshizane K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Loh, T.-P.; Tan, K.-T.; Hu, Q.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (c) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

(10) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319.

Scheme 2 Cyclization of Enantioenriched Alcohol (*S*)-1e



(*S*)-**1e**; 94% ee



+ **1e**; 47%

(-)-**2e**; 32%, 79% ee

tive (*S*)-**1e**, which was readily prepared in 77% yield and 94% ee (Scheme 2). In this case, formation of cation **I** would be less favorable than in the case of **1b** such that tetrahydropyran **2e** produced in the cyclization process would be expected to be enantioenriched. Indeed, treatment of (*S*)-**1e** with propanal, $BF_3 \cdot OEt_2$, AcOH, and TMSOAc gave the 2,4,6-trisubstituted tetrahydropyran (−)-**2e** as the sole product. None of the symmetrical tetrahydropyran **3** was detected indicating that an oxonia-Cope rearrangement is less favored with an electron-deficient aromatic ring. Unlike tetrahydropyran **2b**, in this case the product (−)-**2e** had 79% ee, i.e., only a slightly reduced enantiopurity compared to the starting homoallylic alcohol (*S*)-**1e**.

In conclusion, we have presented results that indicate that the mechanisms of Prins cyclizations are not simple in the cases of homoallylic alcohols possessing an aromatic side chain. The outcome of the reaction is dependent upon the substituents on the aromatic ring. With an electron-deficient aromatic ring, the Prins cyclization proceeds to give the expected 2,4,6-trisubstituted tetrahydropyran **2**, which virtually retains the enantiopurity during the reaction. None of the symmetrical tetrahydropyran **3** is detected. In contrast, with an electron-rich aromatic ring, the symmetrical tetrahydropyran **3** is formed as the major product via a side-chain exchange process and the 2,4,6-trisubstituted tetrahydropyran **2** produced has very low ee (<5%). Various alternative mechanisms to those shown in Figure 2 could be proposed to account for these observations. For example, a pathway involving either an oxonia-Cope rearrangement between **1b** and **5b** would lead to racemization of the starting material or an oxonia-Cope rearrangement of **6** with propanal would racemize **6** and the reversible formation of **III** and cyclization would lead to racemized product **2b**. Further studies are currently underway to investigate the mechanisms of these reactions. In light of these results, care should be taken when using the Prins cyclization in the synthesis of natural products.

Acknowledgment. We thank BBSRC, EPSRC, and AstraZeneca for funding the work.

Supporting Information Available: The preparation and characterization of the compounds described in the paper are included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0102850