

Ring Scission of Cyclic β -Halogeno-ethers with Samarium Di-iodide:

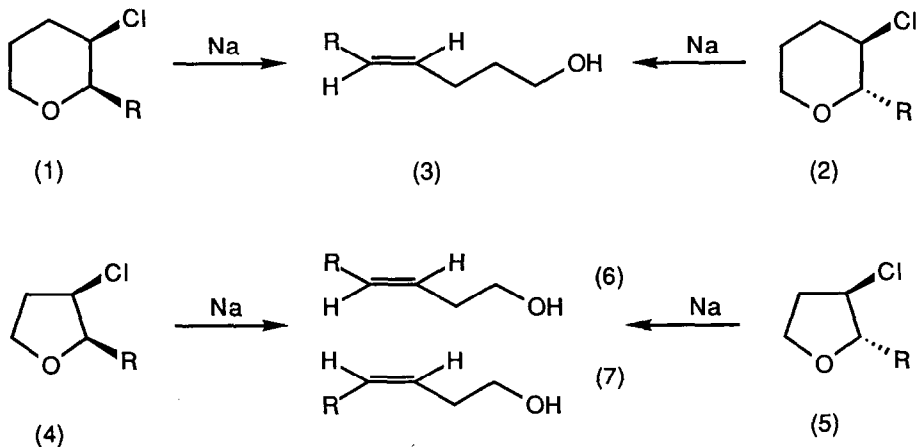
A Synthesis of (E)- and (Z)-Enynols

Leslie Crombie and Linda J. Rainbow

Department of Chemistry, University of Nottingham,
Nottingham, NG7 2RD.

Summary: The use of samarium di-iodide in place of sodium metal for the ring-scission of cyclic β -halogeno-ethers drastically alters the stereochemistry of the resulting olefinic alcohols: using the method, highly stereoselective syntheses of enynols in (Z)- and (E)- forms are reported.

2-Substituted 3-chloro-tetrahydropyrans or -tetrahydrofurans are readily accessible by treatment of the corresponding 2,3-dichloro-compounds with Grignard or other organometallic reagents.¹ The products are often cis-/trans- mixtures but since, in the case of the tetrahydropyrans (1) and (2), each stereoisomer gives almost stereochemically (> 95%) pure (E)- olefinic alcohol (3) on electron transfer with sodium metal, separation of the precursors is not required and the method provides a quick and effective synthesis of (E)-olefinic alcohols.² In the case of the tetrahydrofurans however each stereoisomer (4) and (5) gives a different mixture of (E)-/(Z)- alk-3-enols (6) and (7),² making the reaction of limited preparative use. We have now discovered that samarium



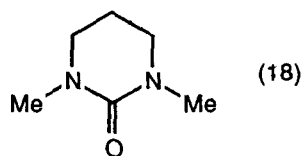
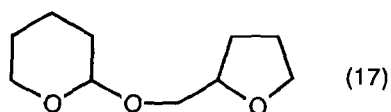
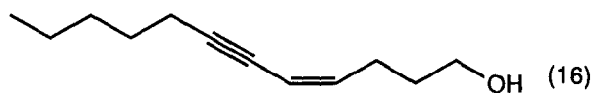
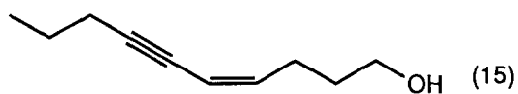
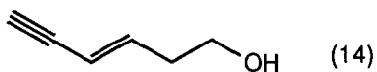
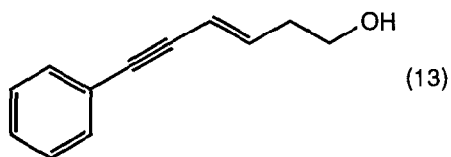
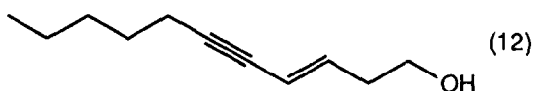
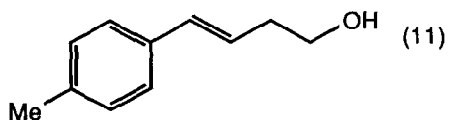
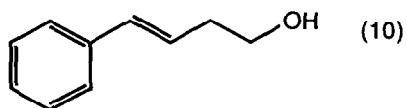
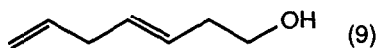
di-iodide in refluxing tetrahydrofuran^{3,4} can carry out the latter scission in good yield (75-90%) with high (> 95%) (E)- stereoselectivity⁵ to give (6,R=Me) from either cis-(4,R=Me) or its trans-isomer (5,R=Me). Similarly an unseparated mixture of (4,R=Et) and (5,R=Et) gave (6,R=Et) in 95% yield with > 98% (E)- stereoselectivity.

Apart from the lack of stereochemical control in the sodium ring scission of (4) and (5), when R=aryl or vinyl the alcohol produced can be badly contaminated with over-reduction products. This difficulty is overcome by using samarium di-iodide. Thus the 2-vinyl derivative (4,R=.CH=CH₂) gave the conjugated dienol (8) in 84% yield with an (E)-content of > 97%. The cis-(67%)/trans-(33%) mixture (4,R=.CH₂CH=CH₂)/(5,R=.CH₂CH=CH₂) gave the methylene-interrupted diene (9) in 93% yield, (E)-content > 97%. Styrene products were isolated from the SmI₂ scission of the trans-isomers (5,R=Ph and R=C₆H₄Mep): in the former case (10) was isolated [yield 95%, (E)-content > 97%] and in the latter (11), yield theoretical, (E)- content > 99%. Over-reduction in these cases was either not observed, or extremely small.

Encouraged by these results, acetylenic cases in the tetrahydrofuran series were examined and found to provide an excellent (E)- enynol synthesis. Thus (4,R=.C≡C.Amⁿ) gave enynol (12) [84%; > 99% (E)-, over-reduction < 1%], (4,R=.C≡C.Ph) gave (13) [75%; > 99% (E), over-reduction < 3%] and (4,R=.C≡CH) gave the terminal enyne (14) [72%, > 99% (E), over-reduction < 5%].⁶ The excellent stereochemical purity of these enynols led us to look at two tetrahydropyran cases. A cis-/ trans- mixture (30:70) of (1,R=.C≡C.Prⁿ) and (2,R=.C≡C.Prⁿ), contrary to our expectation, produced highly stereochemically pure (> 99%) (Z)-enynol (15) in 79% yield. In confirmation, the cis-/trans- mixture of (1) and (2) (20:80) with R=.C≡C.Amⁿ gave (Z)-(16) in 93% yield with stereochemical purity > 97%. We thus have complementary methods of enynol formation giving either the (E)- or (Z)- forms in excellent yields and high stereochemical purity.

On the other hand, SmI₂ mediated ring scission of simple 2-alkyl-3-chlorotetrahydropyrans was less useful than the reaction involving sodium which gives almost pure (E)- olefinic alcohols. Thus the pure cis-isomer (1,R=Et) gave an (E)/(Z) (24:76) mixture of (3,R=Et) and its stereoisomer. The pure trans- isomer (2,R=Et) gave a closely similar (E)/(Z) mixture of alcohols (28:72) suggesting a common intermediate. A cis-/trans- mixture (14:86) of (1) and (2) with R=Prⁱ also gave stereochemically mixed alcohols, (3,R=Prⁱ) and its (Z)- stereoisomer (21:79). Overall yields in these reactions were 85-90%.

SmI₂ ring scission of a mixture of (1,R=D) and (2,R=D) (26:74) gave a mixture of (E)- and (Z)- alcohols (cf. 3,R=D) (53:47). Similarly a mixture of (4,R=D) and (5,R=D) gave a mixture of (6,R=D) and (7,R=D) (49:51). These alcohol ratios again suggest a common intermediate from cis- and trans- precursors and this contrasts with the sodium mediated reaction in which electron transfer and ring scission of the anion are apparently so fast that the stereochemistry of the olefinic alcohols produced correlates with the



stereochemistry and conformation of the original cyclic precursor (i.e. deviation from the Curtin-Hammett principle).² The strikingly different (E)-/(Z)- stereochemistries of product alcohols produced by SmI_2 as compared

with sodium, would appear to be due to complexing effects of the samarium ion with the substrate which are absent in the electron transfer by sodium

A disadvantage of ring scission by SmI_2 is its slowness in refluxing tetrahydrofuran (5 to 165 h) using 4-7 equiv. of SmI_2). The reagent did not form well in 'T-solvent' (17) which would allow higher temperatures, but addition of 5% HMPA to the THF, successful in other reactions of SmI_2 ,⁷ reduced the time for complete ring scission of a mixture of (4,R=Et) and (5,R=Et) (66:34) from 76 h to 9 h in 95% yield with only slight deterioration of the stereochemical quality of the hex-3-enol [92% (E)]. Similar use of the less toxic 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) (18) (10%) in refluxing THF gave a 96% yield of hex-3-enol [$> 93\%$ (E)] in 5 h. Formation of enynol (12) from (4, R=.C \equiv C.Amⁿ) in the presence of DMPU cut the reaction time from 22 h to 3 h [yield 83%, $> 94\%$ (E)]. Unfortunately, although excellent rate accelerations were obtained by adding DMPU, in the two tetrahydropyran cases studied stereochemical control was drastically affected, presumably through complexation changes. The product from a mixture of (1,R=.C \equiv C.Amⁿ) and (2,R=.C \equiv C.Amⁿ) (17:83) was no longer stereochemically homogeneous but a mixture of (Z)-(16) along with its (E)- isomer (63:37) in 90% yield. In the ring scission of the mixed 2-ethyl-3-chlorotetrahydropyrans, the (E)-/(Z)- ratio of products (cf. 3,R=Et) shifted from (23:77) to (87:13).

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References

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2. L. Crombie and R.D. Wyvill, J.Chem.Soc., Perkin Trans.1, 1985, 1983.
3. Our reagent was prepared by Kagan's procedure (J.L. Namy, P. Girard and H.B. Kagan, Nouv.J.Chim., 1977, 1, 5; J.Am.Chem.Soc., 1980, 102, 2693) from samarium and 1,2-di-iodoethane at 20°C under dry nitrogen, with ultrasonication.
4. The reagent has been successfully employed for removing a 2-chloroethyl protecting group (T.P. Ananthanaryan, T. Gallagher and P. Magnus, J.Chem.Soc., Chem.Commun., 1982, 709).
5. Yields and purities assessed by glc and spectral data, with stereochemical purity determined from ¹³Cnmr spectra.
6. Yields are lowered through formation of easily removed dechlorinated precursor in a side-reaction.
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