Pergamon

Tetrahedron Letters 40 (1999) 4319–4320

TETRAHEDRON LETTERS

Base-induced rearrangement of dihydropyran oxides: A novel synthesis of cyclic enol ethers with a hydroxy-function in the allylic position

Bernd Schmidt

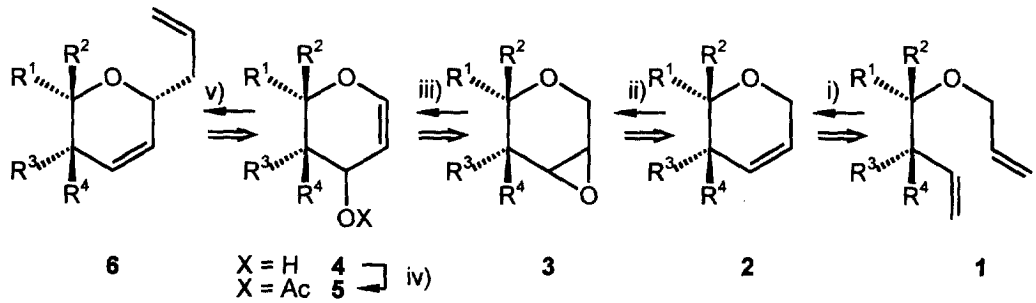
Universität Dortmund, Fachbereich Chemie, Organische Chemie I, D-44221 Dortmund, Germany

Received 13 March 1999; revised 8 April 1999; accepted 16 April 1999

Abstract: A sequence of ring closing metathesis of allyl-homoallyl ethers, epoxidation of the resulting dihydropyrans, and rearrangement of the dihydropyran oxides with LDA provides convenient access to 2,3-dihydropyrans with a hydroxy group in the 4-position. The products may serve as starting materials for e.g. the Carbon-Ferrier rearrangement.

Keywords: metathesis; oxiranes; pyrans; rearrangement.

Cyclic enol ethers play an important role as synthetic intermediates for the construction of various natural products with physiological activity, such as carbohydrates and glycoconjugates,[1-3] *C*-glycosides[4-6] and polyether ionophores[7,8]. The most common synthetic strategies for 2,3-dihydropyrans start from carbohydrates (leading to glycals) or use a *de novo* synthesis starting from aldehydes and siloxydienes which react in a hetero Diels-Alder reaction.[9] Especially 2,3-dihydropyrans with a hydroxy functionality in the 4-position have attracted much interest, as the OH-group can easily be transformed into a leaving group (e.g. acetoxy). Treatment with *C*- or *O*-nucleophiles in the presence of a Lewis-acid opens up an efficient pathway for the stereoselective preparation of *C*-glycosides and glycosides, respectively.[5] In this communication we wish to describe a novel synthesis of 2,3-dihydropyrans with a hydroxy-functionality in the allylic position. The key step is a base induced isomerization of dihydropyran oxides *rac*-**3** to the target molecules *rac*-**4**. Base induced rearrangements of sixmembered ring epoxides have been investigated earlier, however, to the best of our knowledge, this reaction has never been used for the preparation of cyclic enol ethers *rac*-**4**.[10-13]



a:R^2=*p*-anisyl, R^1, R^3, R^4=H; **b**:R^2=$CH(CH_3)Ph$, R^1, R^3, R^4=H; **c**:R^1=phenyl, R^2=Me, R^3, R^4=H; **d**:R^2=Cyclohexyl, R^1, R^3, R^4=H; **e**:R^2, R^3=$(CH_2)_4$, R^1, R^4=H; **f**:R^2, R^3=CH_2OH for **6f** and R^2, R^3=$CH_2OC(Me)_2OCH_2$ R^1, R^4=H (for **1-5f**).

Scheme 1: i) $Cl_2P(Cy_3)_2Ru$=CH-CH=CPh_2 (2 mol%)/DCM, r.t.; ii) MCPBA/DCM, r.t. *or* MMPP/EtOH/H_2O, r.t. *or* DMDO/acetone, 0°C; iii) LDA, THF, 65°C; iv) AcCl, NEt_3, DMAP, DCM, 0°C; v) allyltrimethylsilane, BF_3OEt_2 (1equ.), DCM, -78°C.

Dihydropyran oxides *rac*-**3** were obtained as mixtures of diastereomers from dihydropyrans *rac*-**2**, which are accessible via ring closing metathesis[14] of allyl homoallyl ethers *rac*-**1**.

e mail: bschmidt@citrin.chemie.uni-dortmund.de

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00776-5

Treatment of epoxides *rac*-**3** with LDA is highly regioselective and yields cyclic enol ethers *rac*-**4**. The diastereomeric ratio of products *rac*-**4** resembles the diastereomeric ratio of the starting epoxides, thus, no isomerization occurs afterwards. Epoxides *rac*-**3** can either be employed in diastereomerically pure form (separation of diastereomers is easily achieved by column chromatography) or as mixtures of diastereomers. In the course of our studies directed to the synthesis of *C*-glycosides[15] and polyether compounds we were especially interested in the stereoselective formation of 2,6-disubstituted dihydropyrans *rac*-**6** from enol ethers *rac*-**4**. This transformation is best achieved by Lewis-acid mediated addition of nucleophiles (e. g. allyltrimethylsilane), a reaction which occurs with transposition of the double bond, resulting in the destruction of the stereogenic centre at C-4. Diastereomeric mixtures of dihydropyrans *rac*-**4** can be acetylated and subsequently treated with allyltrimethylsilane in the presence of borontrifluoride etherate to give 3,4-dihydropyrans *rac*-**6** in high yield and very high diastereoselectivity (>95:5, as only one diastereoisomer is detected in the H NMR spectrum of the crude mixtures). Extension of the methodology described herein and application to the synthesis of relevant target molecules is currently under investigation.

*Preparation of dihydropyran rac-cis-**4b**.* Dry diisopropylamine (0.28 mL, 2.0 mmol) is dissolved in dry THF (15 mL) under an argon atmosphere. *n*-BuLi (1.0 M solution in hexane, 2.0 mmol, 2.0 mL) is added at 0°C and the mixture is stirred for 30 min at this temperature. A solution of the diastereomerically pure epoxide *rac-cis*-**3b** (266 mg, 1.3 mmol) is dissolved in dry THF (5 mL) and the solution is added to the reaction flask with a syringe. The mixture is then heated to reflux until the reaction is complete as judged by TLC (hexanes/ether 5:1). Aqueous workup followed by flash chromatography on silica yields diastereomerically pure *rac-cis*-**4b** (190 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.18 (5), 6.33 (dd, 1, J = 6.0, 1.0), 4.67 (ddd, 1, J = 6.3, 2.0, 1.8), 4.38 (dddd, 1, J = 9.3, 6.5, 1.8, 1.5), 4.05 (ddd, 1, J = 11.8, 5.5, 1.8), 2.99 (qd, 1, J = 7.3, 6.5), 2.10 (dddd, 1, J = 12.8, 6.5, 1.8, 1.5), 1.89 (s(br.), 1), 1.47 (ddd, 1, J = 12.8, 11.8, 9.8), 1.34 (d, 3, J = 7.3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.1 (1), 142.6 (0), 128.1 (1), 128.1 (1), 126.5 (1), 105.4 (1), 78.6 (1), 63.4 (1), 43.6 (1), 34.8 (2), 16.5 (3).

Acknowledgment: Generous support of this work by the Fonds der Chemischen Industrie and the DFG is gratefully acknowledged. The author thanks Prof. Dr. P. Eilbracht for encouragement and support.

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