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Regioselective Carbohydroxylation of Enol Ethers by a Photocycloaddition-Hydrogenation Sequence

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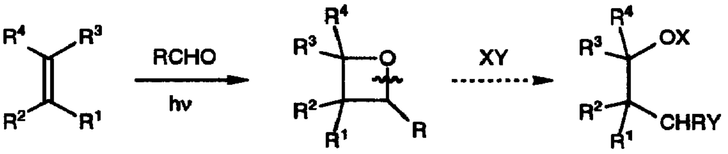
Abstract: It has been shown that enol ether derived 2-phenyl-3-silyloxy-oxetanes **1** and **3** can be cleaved by catalytic hydrogenation. In combination with the preceding Paternò-Büchi reaction the method enables a regioselective access to 1,2-diols **2** starting from olefinic substrates. Optionally, the reduction of **3** can be conducted such that the more hindered tertiary alcohol site in **2** remains silyl-protected.

In the course of the Paternò-Büchi reaction an alkene is converted photochemically to an oxetane ring.[1] As result of the transformation one carbon of the former double bond bears an oxygen atom and the other carbon is connected to an alkyl group. In certain cases it has been observed that the photoexcited carbonyl compounds add regioselectively to the olefinic substrate.[2] If the C-O single bond which has emerged from the carbonyl moiety is subsequently cleaved, this sequence will represent a regioselective carbohydroxylation.

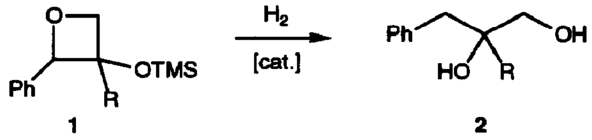


Scheme 1: Regioselective Carbohydroxylation by C-O-Bond Cleavage of Oxetanes

In agreement with related studies[3] we have recently shown that silyl enol ethers are excellent substrates for the Paternò-Büchi reaction with benzaldehyde.[4] The conversion proceeds cleanly to give the corresponding 2-phenyl-3-silyloxy-oxetanes **1** almost exclusively (regioselectivity > 90/10, 45-72% yield). Since it is well documented that benzylic ethers can be readily hydrogenated under metal catalysis[5] we attempted the reductive cleavage of **1**.

As shown in table 1, Pd(0)-catalysis indeed facilitates the desired reaction to yield the alcohols **2**. Typically, the oxetane (1 mmol) was dissolved in 10 ml of methanol and the catalyst was added (0.1 mmol). The hydrogenation was continued until no starting material was detected by TLC. Simple filtration and solvent removal provided an almost quantitative yield of **2**. In order to obtain analytically pure material the crude products were subjected to flash chromatography.[6] The loss of the trimethylsilyl group which occurred during the reduction was anticipated due to its acid sensitivity.

Table 1: Catalytic Hydrogenation of the Oxetanes **1** to the Alcohols **2**



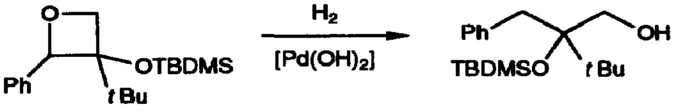
a: Me; **b**: Et; **c**: *i* Pr; **d**: *t* Bu; **e**: Ph; **f**: $CH(OMe)_2$; **g**: $C(OCH_2)_2Me$; **h**: COMe

Entry	Oxetane	Catalyst[a]	Time [h]	Product	Yield[b] [%]
1	**1a**	Pd/C	16	**2a**	86
2	**1b**	Pd/C	16	**2b**	85
3	**1c**	Pd/C	16	**2c**	92
4	**1d**	Pd/C	16	**2d**	88
5	**1e**	Pd/C	24	**2e**	79
6	**1f**	Pd/C	16	**2f**	83
7	**1g**	$Pd(OH)_2$	8	**2g**	86
8	**1g**	Pd/C	16	**2h**	82

[a] 10 mol% of catalyst were employed; [b] after purification by flash chromatography

The ketal **1g** turned out to be labile in the presence of Pd/C and hydrogenolysis afforded the corresponding ketone **2h** (entry 8). Attempts to buffer the solution or to use different solvents in order to avoid deketalization were not successful. However, the protective group could be held in place if the Pearlman catalyst $Pd(OH)_2$ was employed (entry 7).

Reduction of the oxetane **3** which can be generated in 61% yield by a Paternò-Büchi reaction[4b] revealed another advantage of $Pd(OH)_2$ and of the photocycloadditon-reduction sequence, in general (scheme 2). Wheras the reaction proceeded sluggishly with H_2 [Pd/C] causing partial desilylation the TBDMS-protected tertiary alcohol **4** could be conveniently obtained by usage of $Pd(OH)_2$. It is interesting to note that this protocol may provide access to 1,2-diols which carry a protective group at the more hindered hydroxyl site. If further functionalization of the primary alcohol is desired a protection-deprotection strategy commonly applied to 1,2-diols such as **2** can be avoided.



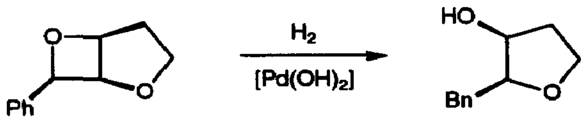
3

4 (79 %)

Scheme 2.

So far, we have only employed C-2 monosubstituted 2-phenyl-oxetanes 1 or 3 as substrates. Remarkably, these compounds are obtained not only with excellent regio- but also with high diastereoselectivity[4] and a possibly useful stereogenic center is consequently destroyed in the course of the hydrogenation. In order to make use of the stereoselection in the photocycloaddition we plan to extend the Paternò-Büchi reaction of silyl enol ethers to unsymmetrical arylketones, e.g. acetophenone. Provided that the stereospecifity of the hydrogenation can be controlled like it is well established in oxirane chemistry[7] the resulting diols may be obtained in diastereomerically pure form.

In addition to our above-mentioned studies the described method can be utilized for the carbohydroxylation of various heterocyclic enol ethers which react regioselectively with carbonylic substrates.[8] Their double bond geometry is transformed stereospecifically into a distinct oxetane configuration which is retained during hydrogenation. An illustrative example is depicted in scheme 3. The known oxetane 5 derived from 2,3-dihydrofuran[9] was reductively cleaved to yield the alcohol 6 as a single diastereoisomer.



5

6 (81 %)

Scheme 3.

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6. Cyclohexane/ethyl acetate (75/25) was mostly used as an eluent. All new compounds were characterized by ^{1}H- and ^{13}C-NMR, IR, MS (EI) and combustion analysis. ^{1}H-NMR data of the diols **2** ($CDCl_3$, 300 MHz):

   2a 1.13 (s, 3H), 2.14 (s, b, 1H), 2.36 (s, b, 1H), 2.77 (d, 1H, J=13.2 Hz), 2.84 (d, 1H, J=13.2 Hz), 3.41 (d, 1H, J=10.9 Hz), 3.48 (d, 1H, J=10.9 Hz), 7.18-7.37 (m, 5H).

   2b 0.95 (t, 3H, J=7.5 Hz), 1.38-1.56 (m, 2H), 2.10 (s, b, 1H), 2.39 (s, b, 1H), 2.79 (s, 2H), 3.44 (s, 2H), 7.15-7.38 (m, 5H).

   2c 0.97 (d, 3H, J=6.8 Hz), 0.99 (d, 3H, J=7.2 Hz), 1.89 (apparent sept, 1H, J=7.0 Hz), 1.98 (m, b, 1H), 2.04 (s, b, 1H), 2.76 (d, 1H, J=13.6 Hz), 2.85 (d, 1H, J=13.6 Hz), 3.42 (dd, 1H, ^{2}J=11.3 Hz, ^{3}J=4.9 Hz), 3.54 (dd, 1H, ^{2}J=11.3 Hz, ^{3}J=5.6 Hz), 7.14-7.33 (m, 5H).

   2d 1.02 (dd, 1H, ^{3}J=8.1 Hz, ^{3}J=4.9 Hz), 1.03 (s, 9H), 2.46 (s, 1H), 2.77 (d, 1H, J=13.6 Hz), 2.95 (d, 1H, J=13.6 Hz), 3.53 (dd, 1H, ^{2}J=11.5 Hz, ^{3}J=8.1Hz), 3.65 (d, 1H, ^{2}J=11.5 Hz, ^{3}J=4.9 Hz), 7.20-7.40 (m, 5H).

   2e 2.17 (dd, 1H, ^{3}J=7.5 Hz, ^{3}J=4.6 Hz), 2.64 (s, 1H), 3.09 (d, 1H, J=13.5 Hz), 3.14 (d, 1H, J=13.5 Hz), 3.71 (dd, 1H, ^{2}J=11.3 Hz, ^{3}J=7.5 Hz), 3.80 (dd, 1H, ^{2}J=11.3 Hz, ^{3}J=4.6 Hz), 6.85-6.97 (m, 2H), 7.10-7.38 (m, 8H).

   2f 2.61 (s, b, 1H), 2.75 (s, b, 1H), 2.79 (d, 1H, J=13.8 Hz), 2.84 (d, 1H, J=13.8 Hz), 3.39 (d, 1H, J=11.3 Hz), 3.49 (s, 3H), 3.53 (s, 3H), 3.69 (d, 1H, J=11.3 Hz), 4.11 (s, 3H), 7.18-7.30 (m, 5H).

   2g 1.39 (s, 3H), 2.66 (dd, 1H, ^{3}J=7.5 Hz, ^{3}J=4.9 Hz), 2.67 (s, 1H), 2.81 (d, 1H, J=13.9 Hz), 3.01 (d, 1H, J=13.9 Hz), 3.41 (dd, ^{2}J=11.7 Hz, ^{3}J=7.5 Hz), 3.60 (dd, 1H, ^{2}J=11.7 Hz, ^{3}J=4.9 Hz), 4.00-4.07 (m, 4H), 7.11-7.32 (m, 5H).

   2h 2.25 (s, 3H), 2.46 (dd, 1H, ^{3}J=9.4 Hz, ^{3}J=3.4 Hz), 2.92 (s, 2H), 3.68 (dd, 1H, ^{2}J=11.7 Hz, ^{3}J=3.4 Hz), 3.92 (dd, 1H, ^{2}J=11.7 Hz, ^{3}J=9.4 Hz), 3.96 (s, 1H), 7.10-7.35 (m, 5H).

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