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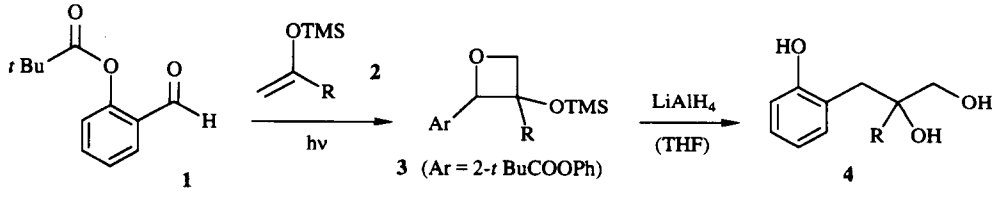
Hydroxyl-Directed Reductive Ring Opening at the C-2 Position of Functionalized 2-Aryloxetanes

Thorsten Bach* and Christian Lange[1]

Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität
Orléansring 23, D-48149 Münster, Germany

Abstract: 2-Aryloxetanes **3** are cleaved at the C-2 position upon treatment with lithium aluminium hydride to deliver the triols **4** in good yields (61-85 %). The regioselective ring opening at the more hindered position is facilitated by a hydoxyl group attached to the arene.

Oxetanes represent versatile C_3-building blocks which can be generated by a wide array of methods.[2] Both carbon atoms adjacent to the ring oxygen are amenable to nucleophilic attack. In non-symmetric oxetanes any ring opening reaction must therefore proceed with good control of regioselectivity to ensure the formation of a single product. Since we have recently shown that silyl enol ether derived functionalized 2-aryloxetanes are available by a diastereo- and regioselective Paternò-Büchi reaction[3,4] we looked into different possibilities to selectively cleave these oxetanes. A regioselective catalytic hydrogenolysis for example is readily accomplished as shown recently.[5] Since some functional groups are not compatible with the conditions employed in this hydrogenolysis we sought after ways to achieve a regioselective ring opening at C-2 by hydride reduction. Most hydride donors approach the oxetane nucleus at the less substituted position via an S_N2 pathway.[6] An S_N1 type mechanism has been postulated for the reaction of AlH_3.[6b] For our example the latter method appeared not suitable due to a readily occurring pinacol type rearrangement upon formation of carbenium ions at the former C-2 of the oxetane.[7] In order to avoid S_N1 conditions we considered a polar substituent at the arene nucleus as a powerful directing group which should faciliate an S_N2 attack by conventional hydride sources at the desired position.



Scheme 1

To this end the 2-pivaloylprotected salicylaldehyde **1**[8] was prepared and converted to the oxetanes **3** by a Paternò-Büchi reaction with the silyl enol ethers **2** (Scheme 1). Upon treatment of **3** with $LiAlH_4$ at 0°C a spot

to spot conversion to the deprotected phenol was observed on TLC. Keeping at room temperature effected a slow (24-72 h) but clean ring opening of the oxetane nucleus and the triol **4** was isolated after work-up (table 1).

Table 1: Preparation of the Ring Opened Products **4**[9] by Photocycloaddition and $LiAlH_4$ Reduction

Entry	R	Oxetane	Yield[a] [%]	Triol	Yield[b] [%]
1	*i* Pr	**3a**	66	**4a**	85
2	Ph	**3b**	61	**4b**	71
3	*t* Bu	**3c**	66	**4c**	61
4	$CH(OMe)_2$	**3d**	63	**4d**	80
5	$C(OCH_2)_2Me$	**3e**	70	**4e**	65
6	CMe_2CHCH_2	**3f**	60	**4f**	64

[a] Yield of the diastereomeric mixture of oxetane **3** after irradiation at 300 nm in benzene (ref. 4a) and purification (flash chromatography). [b] Yield of triol **4** after LAH reduction (3 equiv.) in THF at room temperature and purification (flash chromatography).

Since the phenyl analogues of **3** do not or only sluggishly react with $LiAlH_4$ even at reflux in THF it appears clear that the hydroxyl group liberated in the course of the reaction indeed acts as a directing group. The extension of the described method to 4-substituted oxetanes and further applications are currently studied in our laboratories and will be reported in due course.

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9. ^{1}H-NMR data (300 MHz, $CDCl_3$) for some representative examples **4a**: δ = 1.00 (d, *J* = 6.9 Hz, 6 H), 1.89 (sept, *J* = 6.9 Hz, 1 H), 2.66 (d, *J* = 14.6 Hz, 1 H), 2.97 (d, *J* = 14.6 Hz, 1 H), 3.39 (d, *J* = 11.2 Hz, 1 H), 3.57 (d, *J* = 11.2 Hz, 1 H), 6.87-7.18 (m, 4 H). **4d**: δ = 2.84 (s, 2 H), 3.42 (d, *J* = 11.6 Hz, 1 H), 3.50 (s, 3 H), 3.55 (s, 3 H), 3.82 (d, *J* = 11.6 Hz, 1 H), 4.13 (s, 1 H) 6.82-7.20 (m, 4 H). **4f**: δ = 1.19 (s, 6 H), 2.61 (d, *J* = 14.5 Hz, 1 H), 3.22 (d, *J* = 14.5 Hz, 1 H), 3.58 (d, *J* = 11.9 Hz, 1 H), 3.65 (d, *J* = 11.9 Hz, 1 H), 5.12-5.18 (m, 2 H), 6.11-6.22 (m, 1 H), 6.81-7.18 (m, 4 H).

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