Ruthenium-Catalyzed Flash Oxidation of Allenes to α,α'-Dihydroxyketones

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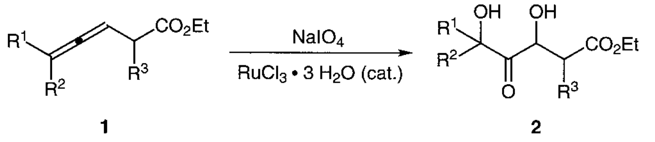
Abstract: The ruthenium-catalyzed flash oxidation of β-allenic esters **1** furnishes α,α'-dihydroxyketones **2** in 24-72% yield. In the case of the chiral allene **1e**, the oxidation proceeds with good diastereoselectivity (88% de), i.e. with efficient axis to center chirality transfer. The flash oxidation can also be used for the synthesis of corticosteroids, as exemplified by the transformation of allenic steroid **4** into dihydroxyketone **5**.

Several different methods are known for the oxidation of allenes.[1-11] Whereas the ozonation leads to the cleavage of the allenic system[1,2], treatment of allenes with dimethyldioxirane[3], peroxides[4], peracids[1,3d,5], and molecular oxygen[6] gives allene mono- and dioxides which are subsequently converted mostly into carbo- and heterocyclic products. Similarly, 3(2H)-furanones are formed in the oxidation of allenic ketones with mercuric acetate.[7] In contrast to this, little is known about the transformation of allenes to acyclic oxidation products. Enones are formed by oxidation of allenes with hypervalent iodine reagents[8], while the treatment with hydrogen peroxide in the presence of tungsten catalysts[9] and with osmium tetroxide[10] furnishes α-hydroxy ketones. There are only few examples for the direct conversion of an allene into the corresponding α,α'-dihydroxyketone by formal dihydroxylation of both allenic double bonds.[3b,11] This transformation, however, is of particular interest because the latter structural element is found in the biologically highly important corticosteroids.[12] Therefore, and due to our interest in syntheses and transformations of functionalized allenes[13], we examined the ruthenium-catalyzed oxidation of β-allenic esters **1** (**Scheme 1**) which are readily accessible by 1,6-cuprate addition to acceptor-substituted enynes.[13] This oxidation method was developed recently for the *cis*-dihydroxylation of alkenes and has been dubbed "flash dihydroxylation" due to its efficiency and short reaction times.[14]



1 **2**

Scheme 1

Application of the original procedure for the dihydroxylation of alkenes[14a] to allene **1a**, i.e. treatment of a solution of the substrate in EtOAc/MeCN (1:1) at 0°C with 10 mol-% of $RuCl_3 \cdot 3\ H_2O$ and 3.0 eq. of $NaIO_4$ (1.5 eq. per allenic double bond) in water, provided the desired oxidation product **2a**[15] with 32% yield (**Table 1**). The starting material was consumed completely within 5 minutes; thus, the oxidation of allene **1a** takes place with a similar rate as the flash dihydroxylation of alkenes.[14] Other reaction products could not be detected; presumably, over-oxidation leads to fission products (aldehydes and ketones) which are highly volatile and/or unstable. This assumption is confirmed by the observation of acetophenone as only reaction product (59% yield) upon treatment of the phenyl-substituted allene **1b** under these conditions. Similar to **1a**, flash oxidation of the sterically crowded allene **1c**[16] gave the dihydroxyketoester **2c** with 24% yield (again as only isolable product).

The flash oxidation procedure was also applied to chiral allenes bearing two different substituents at C-5. In these cases, two new centers of chirality are formed at the expense of the chirality axis of the allene; i.e. the reaction could proceed diastereoselectively with axis to center chirality transfer.[2b] The flash oxidation of allene **1d** under the above conditions furnished product **2d** with a good yield of 72% as a 1:1 mixture of diastereomers. The diastereoselectivity could be improved slightly to 55:45 (10% de) by decreasing the amount of sodium periodate to 1.5 eq.; in this case, only 50% of the starting material was consumed, and the yield of **2d** was 52% (with regard to consumed **1d**). Further variations of the stoichiometry of the reactants and of the order of addition gave no improvement of yield and selectivity. For example, the reaction proceeded much slower when acetonitrile[14b] was used as organic solvent instead of EtOAc/MeCN (1:1), and large amounts of over-oxidation products were formed.

Table 1: Ruthenium-catalyzed flash oxidation of allenes **1**.

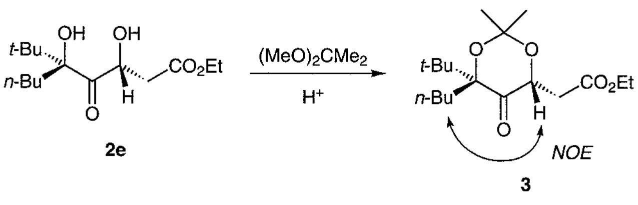
Allene	R^1	R^2	R^3	Product	Yield (%)	de (%)
1a	Me	Me	H	**2a**	32	–
1b	Ph	Me	H	–[a]	–	–
1c	*t*-Bu	*t*-Bu	H	**2c**	24	–
1d	*t*-Bu	Me	H	**2d**	72	0
1d	*t*-Bu	Me	H	**2d**	52[b]	10[b]
1e	*t*-Bu	*n*-Bu	H	**2e**	38	88
1f	*t*-Bu	Me	OEt	**2f**	45	c

[a] Formation of acetophenone; see Text. [b] With 1.5 eq. of NaIO4; see Text. [c] Three diastereomers; see Text.

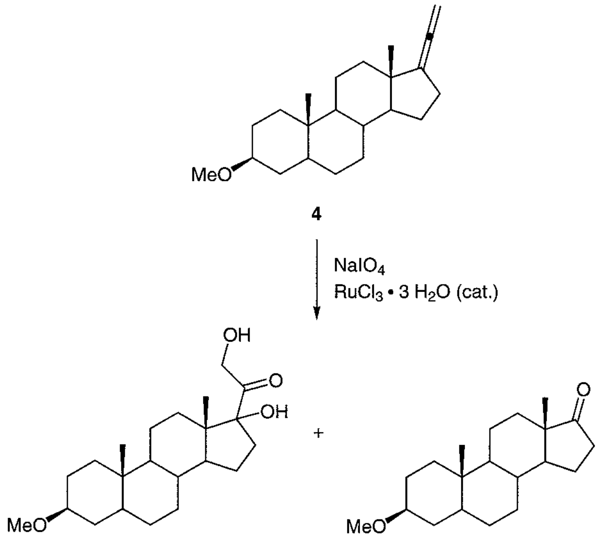
In contrast to this, the reaction of allene **1e** (bearing a *t*-butyl and a *n*-butyl group at C-5) under the original conditions (3.0 eq. of $NaIO_4$) gave the product **2e** with 38% yield and a good diastereoselectivity of 94:6 (88% de; both isomers were obtained in pure form by column chromatography). Thus, the ruthenium-catalyzed flash oxidation of allenes constitutes another case of efficient axis to center chirality transfer.[2b] Similarly, the ethoxy-substituted allenic ester **1f** (1:1 mixture of diastereomers) gave the oxidation product **2f** (bearing five different oxygen functionalities at adjacent carbon atoms!) with 45% yield as a 48:38:14 mixture of three diastereomers. In these reactions, racemic allenes **1d**-**f** were employed; however, the allenes can also be synthesized enantioselectively[2b], and consequently the oxidation products are also accessible in diastereo- and enantiomerically enriched form.

In order to assign the relative configuration of dihydroxyketoester **2e**, the major diastereomer was converted into the acetal **3** by treatment with 2,2-dimethoxypropane (**Scheme 2**). A NOE effect between the hydrogen atom at C-3 and the first CH_2 group of the *n*-Bu substituent was observed, confirming a (3*SR*,5*RS*) configuration for **3** and **2e**.

Finally, we applied the flash oxidation procedure to the allenic steroid **4** (prepared from epiandrosterone according to literature procedures[17]) in order to establish whether this method can also be used for the one-step preparation of corticosteroids (**Scheme 3**). A chromatographically separable mixture of the desired product **5** (16% yield) and the ketone **6** (49%) was obtained.



Scheme 2



Scheme 3

Whereas the substrates **1** possess a trisubstituted allenic system, the terminal allene **4** is only disubstituted, and in this case oxidative cleavage of the unsaturation prevails. Nevertheless, this example shows that the ruthenium-catalyzed flash oxidation of allenes can also be applied to target molecules of biological relevance and that further improvements of the method (e.g., by using non-aqueous conditions and lower temperatures) have to be developed in order to increase its efficiency. Further work along these lines is in progress.

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(15) Representative experimental procedure: A solution of 250 mg (1.6 mmol) of **1a** in 6 ml each of acetonitrile and ethyl acetate was cooled to 0°C, and a suspension of 1.04 g (4.9 mmol) of $NaIO_4$ and 42 mg (0.16 mmol) of $RuCl_3 \bullet 3\ H_2O$ in 2 ml of water was added. After stirring at 0°C for 5 min 2 ml of a saturated aqueous $Na_2S_2O_3$ solution was added, the mixture was filtered through Celite and the crude product was purified by column chromatography (SiO_2, cyclohexane/diethyl ether, 1:1). Yield: 104 mg (32%) of **2a** as a colorless oil.
Spectroscopic data of **2a**: ^{1}H-NMR: δ = 1.19 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.36/1.37 (2s, 6H, 5-CH_3), 2.73 (dd, J = 16.2/6.9 Hz, 1H, 2-H), 2.90 (dd, J = 16.2/4.4 Hz, 1H, 2-H), 3.75/4.09 (2s, 2H, OH), 4.09 (d, J = 7.1 Hz, 2H, OCH_2), 4.87 (m, 1H, 3-H). ^{13}C-NMR: δ = 14.0 (+, OCH_2CH_3), 26.9/27.7 (2+, 5-CH_3), 38.6 (-, C-2), 61.1 (-, OCH_2), 70.9 (+, C-3), 77.7 (x, C-5), 171.7 (x, C-1), 214.1 (x, C-4). IR: ν = 3600-3200 (O-H), 1732 (C=O), 1717 cm^{-1} (C=O). MS: m/e (%) = 205 (<1, M^++1), 118 (100). Calcd. for $C_9H_{16}O_5$: C 52.93, H 7.90; found C 52.62, H 8.01.

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