Pergamon

Tetrahedron Letters, Vol. 35, No. 10, pp. 1489-1492, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0074-B

Oxidative Cyclizations of Allenic Aldehydes

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Abstract: Allenyl aldehydes and ketones are oxidatively cyclized by dimethyldioxirane to provide cyclic acetals and hemiacetals.

Several years ago in our continuing examination of the epoxidation of allenes,[1] we showed that dimethyldioxirane (**DDO**) provides access to the fragile diepoxides of allenes, owing to the neutral, non-nucleophilic conditions of such oxidations.[2] **DDO** oxidations of allenes bearing nucleophilic groups led to highly functionalized oxygen heterocycles derived from cyclization of intermediate mono- and diepoxides.[3,4] Since **DDO** oxidizes aldehydes to acids,[5] oxidation of allenic aldehydes was examined as a potential source of lactones of the type formed from acids.[4] In fact, aldehyde oxidation is generally slower than that of the allene and products are derived from opening of transient epoxides by nucleophilic participation of the aldehyde.

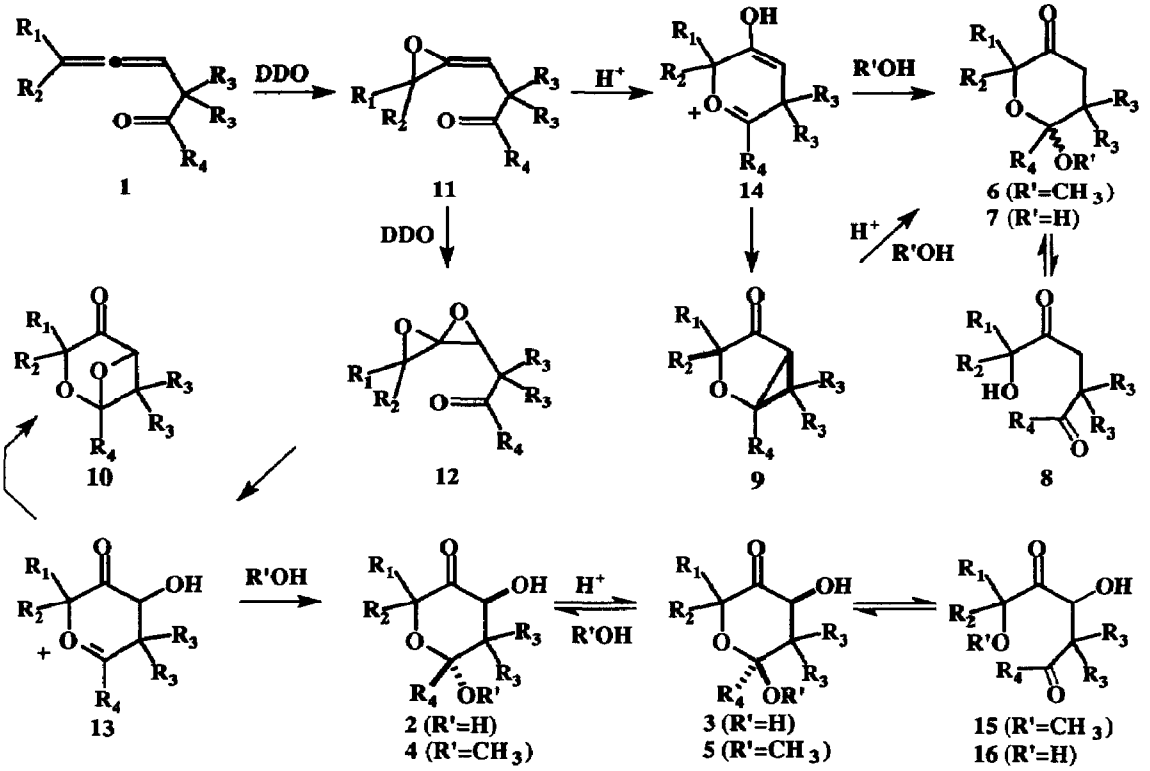
β-Allenyl aldehyde **1a** reacted with an excess of **DDO** in moist acetone to give a 1:1 mixture of anomers **2a** and **3a** in 83% yield (Scheme 1).[6] Oxidation of **1a** using rigorously dried **DDO** solutions in the presence of methanol and anhy K_2CO_3 gave one cyclic acetal (83% yield) assigned as *trans* anomer **4a**. This is a kinetic product, since heating **4a** with methanol and *p*-toluenesulfonic acid (TsOH) generated a 28:72 mixture of **4a** and *cis* isomer **5a**.[7] Non-hydroxylated acetal **6a** was produced in 80% yield upon adding a solution of TsOH in the **DDO** reagent to **1a** in methanol/CH_2Cl_2/powdered 3Å mol. sieves. Oxidation in the presence of TsOH•H_2O in CH_2Cl_2 gave hemiacetal **7a**, in equilibrium with open-chain isomer **8a** in $CDCl_3$. Especially dry **DDO** in the presence of powdered mol. sieves, but without a nucleophile, gave a mixture of bicyclic compounds **9a** (31%) and **10a** (59%). Bridged acetal **10a** was converted by TsOH/methanol to a mixture of the anomeric acetals **4a** (28%) and **5a** (68%). Cyclopropyl ketone **9a** was cleaved to 2,2-dimethyl-4-(1'-methyl-1'-methoxyethyl)-3-oxacyclopentanone (70% yield) under the same conditions. Interestingly, *in situ* oxidation of **1a** (CH_2Cl_2/acetone/aq $NaHCO_3$/Oxone) also generated cyclopropyl ketone **9a** (60% yield).

Oxidation of 1,3-disubstituted allenic aldehyde **1b** in the presence of methanol gave a single, *trans* [7] cyclopropyl ketone **9b** (32%), along with the two diastereomeric acetals (4:1 ratio of *trans,trans* to *cis,trans*)[7] of structure **4b**.[6] **DDO** oxidation without added nucleophile (mol. sieves) produced **9b** and bicyclic acetal **10b**

(1.6:1 mixture of stereoisomers). A mixture of **9b** and **10b** was also obtained from an *in situ* oxidation. Internal cyclopropyl bond rupture of **9b** resulted upon TsOH/methanol treatment to give anomeric acetals **6b** (72%).[6,7] Similar reaction of bicyclic acetal **10b** generated the four acetals of structure **4b** and **5b**. Finally, **DDO** oxidation of **1b** in the presence of $TsOH{\cdot}H_2O/CH_2Cl_2$ led to anomeric hemiacetals **7b** (72%; 3:1 ratio).[6]

In contrast, ß-allenyl aldehyde **1c** was slowly oxidized to the corresponding allenic acid (72%). The lower reactivity of the monosubstituted allene group by **DDO** results in preferential oxidation of the aldehyde.

SCHEME 1



a: $R_1{=}R_2{=}R_3{=}CH_3$, $R_4{=}H$; **b:** $R_1{=}n$Pr, $R_2{=}R_4{=}H$, $R_3{=}CH_3$; **c** $R_1{=}R_2{=}R_4{=}H$, $R_3{=}CH_3$; **d:** $R_1{=}R_2{=}R_4{=}CH_3$, $R_3{=}H$; **e:** $R_1{=}R_2{=}R_3{=}R_4{=}CH_3$

Oxidative cyclizations of the β-allenyl aldehydes are rationalized in Scheme 1 *via* sequential **DDO** oxidation to allene oxides **11** and diepoxides **12**. The indicated structure of **11** is expected when the allene terminus is disubstituted, whereas this species is undoubtedly accompanied by its internal regioisomer when the allene terminus is monosubstituted. Product evolution can occur from either mono- or diepoxides. In each case, nucleophilic involvement of the aldehyde accompanies opening of the epoxide intermediate.[8] Thus, products from the diepoxide are formed *via* cation **13**. Capture of **13** by water leads to equilibrating

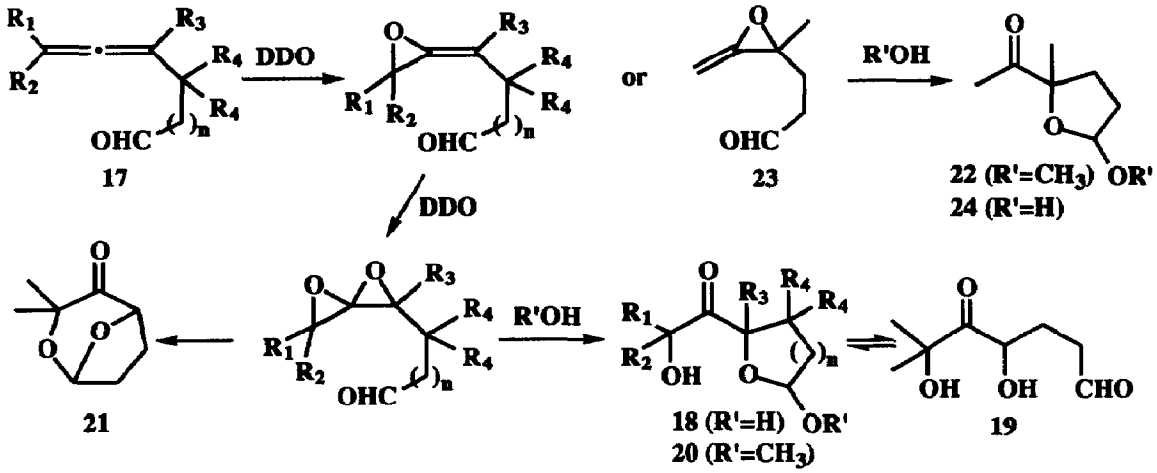
hemiacetal anomers **2** and **3**, whereas methanol trapping is kinetically controlled by the anomeric effect,[9] which favors axial attack on a preferred conformation of **13** and results in a *trans* relationship between the methoxy and hydroxy groups as shown in **4**. It is difficult to rationalize this stereochemistry without invoking stereoselective capture of cation **13**. In the absence of an external nucleophile, the α-hydroxy group traps the positive charge intramolecularly to give **10**. Products can also be formed at the monoepoxide stage. In the presence of acid, a species such as **14** provides a logical link to **6** and **7**. Cyclopropyl ketones **9** are formed by a related process, perhaps involving the zwitterionic analog of **14**.

β-Allenyl ketones give analogous cyclic products. Thus, reaction of DDO with methyl ketone **1d** in methanol (mol. sieves) generated a single acetal assigned as *trans* anomer **4d** (47%) and open-chain methoxy ketone **15d** (27%). Oxidation with moist DDO gave acyclic diketones **8d** (58%) and **16d** (29%) derived from mono- and di-oxidation of **1d**, respectively. These ketones exist entirely in the open form. Oxidation of the *gem*-dimethyl derivative **1e** in methanol produced cyclopropyl ketone **9e** (25%) and a single cyclic acetal (60%), presumably *trans* isomer **4e**. In this hindered situation, cyclopropane formation is competitive.

The regiochemistry of cyclization is reversed with γ- and δ-allenyl aldehydes, so as to generate five- and six-membered rings (Scheme 2). Thus, γ-allenyl aldehyde **17a** is converted by moist DDO to anomeric hemiacetals **18a** (68%), which were further oxidized to the known γ-lactone.[4,10] Hemiacetals **18a** are in equilibrium with open isomer **19**. In the presence of methanol, DDO treatment of **17a** gave a single acetal (51%), assigned as the *trans* isomer of **20a**, on the basis of steric control in the addition of methanol. Dry DDO gave bicyclic acetal **21** as the only stable product isolated from **17a**, albeit in low yield (17%). Terminal allene **17b** was oxidized by DDO in methanol to a mixture of acetals **22** (35%) and **20b** (38%),[6] each as an anomeric mixture. The formation of **22** is consistant with initial epoxidation at the more-substituted internal site of this particular allene to give **23** as the first intermediate. Oxidation of **17b** with moist DDO gave anomeric hemiacetals **18b** (42%). On the other hand, reaction with DDO in the presence of TsOH diverted the allene oxide to cyclic hemiacetal **24** (61%). Unfortunately, these oxidative cyclizations were not very stereoselective, as demonstrated with the 1,3-disubstituted allene **17c**, which afforded a mixture (90%) of all four stereoisomers of **18c** upon DDO oxidation. Finally, wet DDO reagent gave a low yield (38%) of hemiacetal mixture **18d** from δ-allenyl aldehyde **17d**. This structure was confirmed by oxidation to the δ-lactone.[10] These transformations are once again readily understood in terms of intermediate allene mono- and diepoxides as illustrated in Scheme 2. The partitioning to products depends both on the structure of the allene and the reaction conditions .

In conclusion, the oxidative cyclizations of allenic aldehydes provide a novel and efficient route to highly functionalized cyclic heterocycles of potential interest in the synthesis of sugar-like molecules.

SCHEME 2



a: $R_1=R_2=CH_3$, $R_3=R_4=H$, n=1; **b:** $R_1=R_2=R_4=H$, $R_3=CH_3$, n=1;
c: $R_1=n$Pr, $R_2=R_3=H$, $R_4=CH_3$, n=1; **d:** $R_1=R_2=CH_3$, $R_3=R_4=H$, n=2

Acknowledgments: This work was supported in part by a grant from the PHS (GM-39988). ER was the recipient of a GANN fellowship from the DoEd; JKC thanks the Université de Paris-Sud for a visiting professorship during which time this article was prepared.

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(6) Characterized as the benzoate: PhCOCl, Et_3N, CH_2Cl_2.

(7) This stereochemistry was assigned by appropriate NOE difference experiments.

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(10) Oxidation by pyridinium dichromate in CH_2Cl_2.

(*Received in USA* 1 *December* 1993; *accepted* 20 *December* 1993)