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Oxidative Cyclizations of Allenic Sulfonamides with Dimethyldioxirane

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Abstract: The dimethyldioxirane oxidations of allenic amine derivatives give highly functionalized nitrogen heterocycles derived from cyclizations of intermediate allene mono- and diepoxides.

As part of our continuing studies on the oxidation chemistry of allenes,[1] we have shown that dimethyldioxirane[2] (**DDO**) is a particularly useful reagent for the generation of allene diepoxides (spirodioxides) by rapid, sequential epoxidation under conditions which these fragile products survive. **DDO** oxidations of allenes bearing alcohol[3] and acid[4] groups resulted in highly functionalized oxygen heterocycles derived from nucleophilic cyclizations of intermediate mono- and diepoxides. In this contribution we examine the possibility of performing such "oxidative-cyclizations" with internal nitrogen nucleophiles as a route to highly functionalized nitrogen heterocycles. In view of the known reactivity of amines towards **DDO**,[2,5] we have chosen to use the sulfonamide group as a less readily oxidized, but still nucleophilic, nitrogen function.

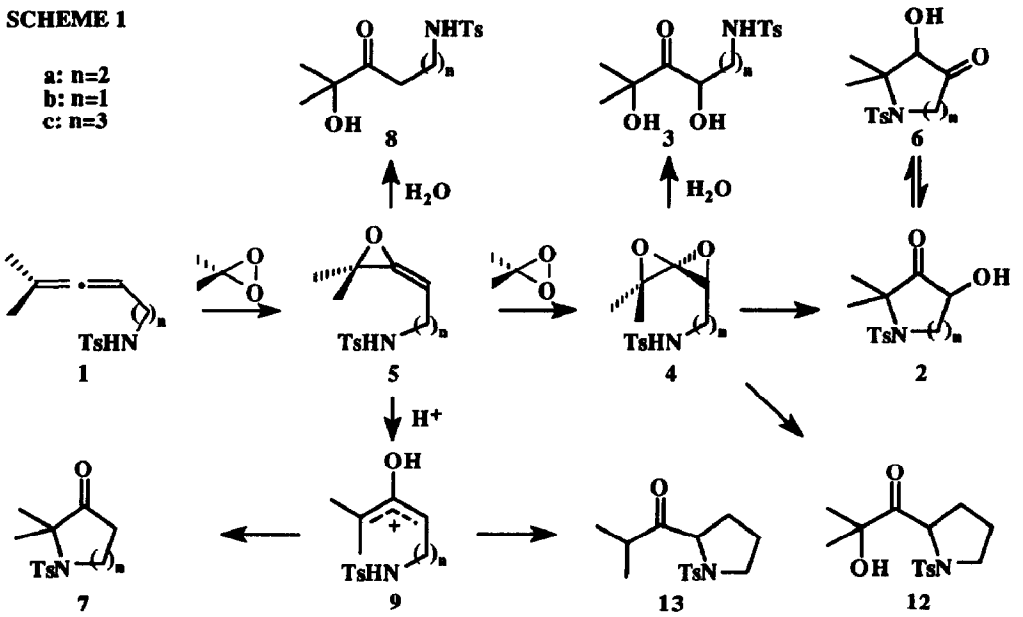
It was convenient to perform the **DDO** oxidations of allenic sulfonamides **1** with a large excess of the cold oxidant solution in acetone[6] until TLC analysis indicated the disappearance of **1**, at which time the excess oxidant was removed and the products were isolated by preparative TLC. The β-allenyl sulfonamide **1a**[7,8] was converted by **DDO** (7.5 equiv) in this manner to hydroxypiperidone **2a**[8] (52% isolated yield) and a little dihydroxy ketone **3a**. Because of an unusually large coupling constant (J = 9.5 Hz) of the proton on the hydroxylated carbon with *each* of the adjacent methylene protons, the assignment of **2a** was verified by an X-ray structure.[9] A mixture of **2a** and **3a** (3:2) was also obtained from an *in situ* oxidation, in which **1a** was oxidized in buffered aqueous acetone by a large excess of Oxone under the conditions used to prepare **DDO**. Although the isolated yield of **2a** (38%) is lower, this procedure is more readily scaled-up and avoids the inconvenience of isolating the **DDO** reagent. These results are nicely rationalized by a sequence involving step-wise epoxidation of **1a** to spirodioxide intermediate **4a**, which then undergoes regioselective nucleophilic opening by the internal sulfonamide to yield **2a** or bimolecular attack by water to give **3a**. The initial epoxidation is expected to generate allene oxide **5a** by preferential **DDO** attack at the more highly substituted

double bond, *anti* to the side-chain.[1] This defines the stereochemistry of spirodioxide **4a**, which is appropriate for intramolecular reaction. It is interesting that the *in situ* oxidation of **1a** gives products derived from **4a**, since this method usually involves product formation at the monoepoxidation stage.[3,4]

The purification of **2a** by chromatography was complicated by its rearrangement to isomer **6a**[8] by the ketol transposition previously observed for related structures.[3,4] In fact, clean conversion of **2a** to **6a** (51%) could be effected by stirring with a slurry of silica gel in $CHCl_3$-ether. This indicates that the structural arrangement in **6a** is significantly more stable than that of **2a**.

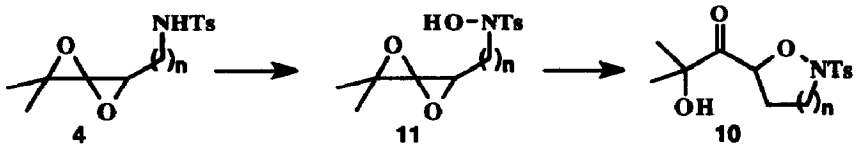
SCHEME 1

a: n=2
b: n=1
c: n=3



The diversion of allene oxide **5a** to stable products was achieved by slowly adding **DDO** (3 equiv) containing an equiv of *p*-toluenesulfonic acid (TsOH) to a CH_2Cl_2 solution of **1a**, which produced a mixture of piperidone **7a**[8] (23%) and acyclic hydroxyketone **8a** (33%). This result is understood in terms of irreversible acid-promoted opening of **5a** to hydroxyallyl cation **9a**, which undergoes internal sulfonamide or external water attack, followed by tautomerization to the observed products. By contrast, oxidation of **1a** with **DDO** (8.5 equiv) in the presence of a large amount of solid K_2CO_3 generated a 1:1.6 mixture of **2a** and isoxazolidine **10a**[8] (47% isolated). The formation of **10a** was unexpected and clearly involves an additional oxidation step. This presumably occurs at the sulfonamide site, probably after allene oxidation, to produce a hydroxylamine derivative such as **11a**. Cyclization by intramolecular attack of the hydroxylamine on the

spirodioxide gives **10a**. The function of K_2CO_3 is to generate the sulfonamide anion, the species actually being oxidized by **DDO**. The reversal in cyclization regiochemistry is controlled by ring-size preferences.

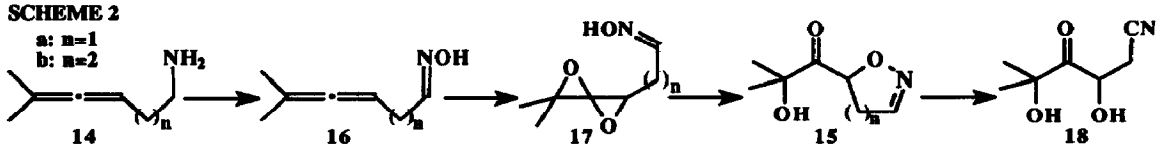


DDO oxidation (8 equiv) of the α-allenyl sulfonamide **1b**[8,10] yielded **2b**[8] as the major product (56%) along with a little **3b**. An *in situ* oxidation with excess Oxone also gave **2b** (67%). In both cases, **2b** was contaminated by a small amount of a similar material assigned as isomer **6b** on the basis of spectral data and of the conversion of **2b** to a 5:2 mixture of **2b:6b** upon stirring with silica gel in $CHCl_3$-ether. Oxidation of **1b** in the presence of TsOH generated pyrrolidone **7b**[8] (42%) plus minor amounts of **8b**.

γ-Allenyl sulfonamide **1c**[7] was converted to a mixture of acyclic spirodioxide rearrangement products[1] under the usual oxidation conditions, but reaction in the presence of solid $NaHCO_3$ with **DDO** (9 equiv; dried over K_2CO_3) yielded pyrrol **12**[8] (64%). An *in situ* oxidation with added K_2CO_3 also gave **12** (57%). **DDO** oxidation (3 equiv) in the presence of TsOH diverted **1c** to pyrrol **13**[8] (81%) accompanied by a little **12**. Finally, the use of **DDO** (9 equiv) with solid K_2CO_3 led to a mixture of **13** (67%) and tetrahydrooxazine **10c**[8] (13%). These products are derived in an analogous manner to that discussed above with cyclization occuring at the proximal carbon of the intermediate allene oxides to generate favored five- and six-membered rings.

Several **DDO** oxidations were also performed on the free primary amines **14**, but these were complicated by oxidation of the nitrogen center. Thus, treatment of **14a**[5] with **DDO** (10 equiv) in the presence of solid $NaHCO_3$ gave isoxazoline **15a**[8] as the only significant product, albeit in only 21% isolated yield. A better yield (34%) of **15a** was obtained by **DDO** (6.7 equiv) oxidation of a 1:1 mixture of **E**- and **Z**-allenic oximes **16a**[5]. In view of our earlier demonstration[5] that oxime **16a** can be obtained from **14a** with smaller amounts of **DDO**, it is clear that **15a** is formed by oxidative cyclization of **16a** *via* spirodioxide **17a** by a process involving nucleophilic attack of the oxime oxygen. Only the **Z** isomer can cyclize in this manner, which may account for the poor yield of **15a**, given that geometrical isomerization of the oximes may be slow

SCHEME 2



relative to other reaction processes.[11] Interestingly, a similar reaction using solid K_2CO_3 gave a mixture of **15a** and nitrile **18**,[8] which was shown to result from K_2CO_3-promoted fragmentation[12] of **15a** (53%). γ-Allenyl amine **14b**[13] behaved in an analogous manner, giving dihydroxazine derivative **15b**[8] (21%) as the only isolated product of **DDO** oxidation. A sequence *via* oxime **16b** and spirodioxide **17b** accounts for **15b.**

In conclusion, several interesting, highly functionalized heterocyclic systems are generated by the **DDO** promoted oxidative cyclizations of allenic amine derivatives.

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(6) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(7) Prepared from the corresponding amine: TsCl, NEt_3, DMAP, CH_2Cl_2.

(8) Characterized by IR, ^1H and ^{13}C NMR; elemental composition by combustion or high-resolution mass spectromety.

(9) This crystal structure showed disorder attributed to the presence of equal amounts of two conformers differing mainly in the position of the carbinol carbon in a chair-like and a boat-like form. A similar situation in solution could account for the unusual vicinal coupling constants found for **2a.**

(10) Prepared from the corresponding alcohol by the procedure of Henry, J. R.; Marcin, L.R.; McIntosh, M. C.; Scola, P.M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett. 1989, 30,* 5709.

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(13) Prepared by $LiAlH_4$ reduction of the corresponding nitrile; Delair, T.; Doutheau, A.; Goré, J *Bull. Soc. Chim. Fr.* **1988**, 125.

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