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Double Deprotonation of Acetylenic Oxiranes: Synthesis of Allenic Ketones through Dilithio Ynenolates

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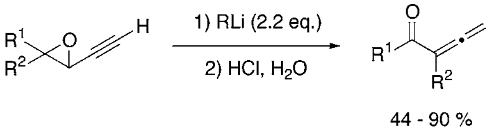
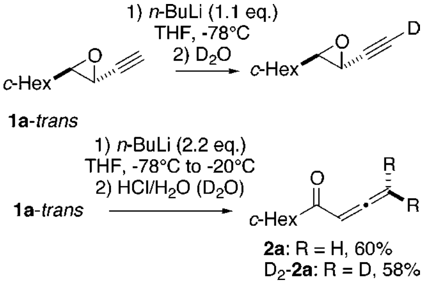
ABSTRACT



The double deprotonation of acetylenic oxiranes gives allenic ketones through the 1,2-H or 1,2-Ar shift on the transient oxiranyl dianion intermediates. The resulting dilithium ynenolates give allenic ketones upon hydrolysis or can be quenched with various electrophiles.

We have recently reported that ring-opening reaction of acetylenic oxiranes with organolithium reagents in the presence of BF_3•Et_2O occurs smoothly only at the propargylic center with pure inversion of configuration.[1] In the course of these studies, we have serendipitously discovered the unprecedented reaction of acetylenic oxirane **1a**-*trans* with *n*-BuLi. Deprotonation at the acetylenic position occurs normally by the reaction of **1a**-*trans* with *n*-BuLi (1.1 equiv) as shown through quenching with D_2O (Scheme 1). By contrast, the reaction of **1a**-*trans* with 2.2 equiv of *n*-BuLi leads surprisingly to allenic ketone **2a** upon hydrolysis. A double deuteration was observed through quenching with D_2O, and the dideuterated ketone D_2-**2a** was obtained with more than 95% D-incorporation on the two terminal allenic positions (based on ^1H NMR analysis).

Scheme 1



The formation of ketones from oxiranes has been described several times in the literature through the rearrangement of oxiranyl anion intermediates.[2] Two possible mechanisms have been reported (Scheme 2), involving a 1,2-H shift[3] (path a) or an electrocyclic ring opening[4] (path b), and depending on the structure of the oxiranyl anion intermediate. In our

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[3] (a) Thummel, R. P.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 4250−4254. (b) Thies, R. W.; Chiarello, R. H. *J. Org. Chem.* **1979**, *44*, 1342−1344. (c) Hodgson, D. M.; Robinson, L. A.; Jones, M. L. *Tetrahedron Lett.* **1999**, *40*, 8637−3640.

[4] (a) Cope, A. C.; Trumbull, P. A.; Trumbull, E. *J. Am. Chem. Soc.* **1958**, *80*, 2844−2849. (b) Crandall, J. K.; Chang, L. H. *J. Org. Chem.* **1967**, *32*, 435−439. (c) Thummel, R. P.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 3919−3923. (d) Yaganisawa, A.; Yasue K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103−2104. (e) Capriati, V.; Florio, F.; Luisi, R.; Russo, V.; Salomone, A. *Tetrahedron Lett.* **2000**, *41*, 8835−8838.

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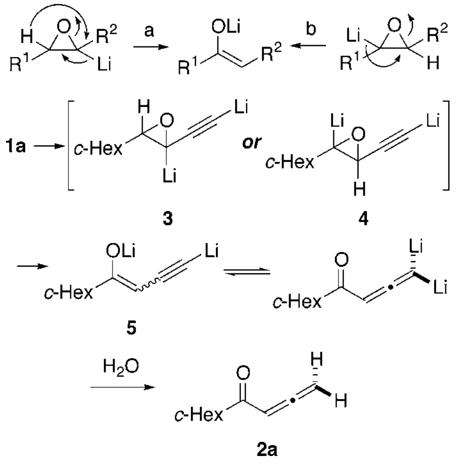
Scheme 2

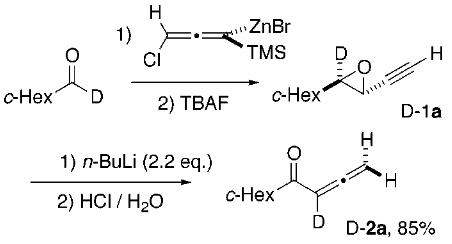


case, this rearrangement should necessarily occur through the formation of a *dilithiated oxirane intermediate*. The structure of this dianion was then questioned.

Deprotonation can occur at the propargylic position leading to dianion **3**, followed by a 1,2-H shift to give the dilithium ynenolate **5**. This deprotonation could be favored due to the electronic influence of the triple bond. However, this influence should be considerably modified by the anterior acetylenic deprotonation. Alternatively, the deprotonation could occur at the homopropargylic oxiranyl center, leading to dianion **4**, which could undergo an electrocyclic ring opening to give **5**. In both cases, the same dilithium ynenolate **5** would be formed, giving allenic ketone **2a** upon hydrolysis. From all the possible isomeric forms of the dilithium species formed through the rearrangement step, the *O*,*C*-dilithium acetylenic species **5** seems to be the most probable.

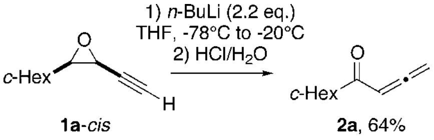
To determine which of the two above depicted mechanisms is followed, we have conducted the reaction on the deuterated oxirane D-**1a**-*trans*, prepared from 1-*D*-cyclohexanecarbaldehyde using our allenylzinc methodology[5] for the preparation of acetylenic oxiranes (Scheme 3). We obtained under the same conditions only deuterated allenic ketone D-**2a** (>98% D-incorporation), showing thus unambiguously that the mechanism of our transformation follows only the path a in Scheme 2, i.e., deprotonation on the propargylic oxirane center and subsequent 1,2-H (in this case 1,2-D) shift.

Scheme 3



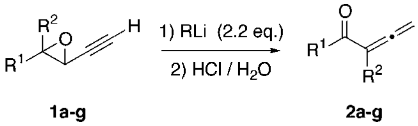
It must be concluded that the first deprotonation at the acetylenic position slows down but surprisingly does not inhibit the second deprotonation[6] at the propargylic position. The first deprotonation occurs quickly at −78 °C, whereas the second one takes place slowly at −20 °C. This can be compared to the behavior of similar acetylenic oxiranes bearing a TMS group at the acetylenic terminus.[7] These compounds have been shown to undergo rapid deprotonation at the propargylic center at −90 °C. However, all our attempts to quench the dianion failed. The rearrangement seems to occur immediately after the second deprotonation. Interestingly, no difference in reactivity was observed starting from the acetylenic oxirane **1a**-*cis* compared to the **1a**-*trans* isomer, as under the same conditions the same allenic ketone **2a** was obtained in a similar yield (Scheme 4).

Scheme 4



We have examined the scope and limitations of our reaction with various acetylenic oxiranes (Table 1). The starting materials were prepared (as described above for D-**1a**) by the condensation of various aldehydes or ketones with the allenylzinc derived from 3-trimethylsilyl propargyl chloride[5] and subsequent quantitative desilylation/ring closure

Table 1. Synthesis of Allenic Ketones[8] from Acetylenic Oxiranes



entry	oxirane	R	R^1	R^2	yield[a] %
1	**1a**-*trans*	*n*-Bu	*c*-Hex	H	87 (60)
2	**1a**-*cis*	*n*-Bu	*c*-Hex	H	(64)
3	**1b**[b]	*n*-Bu	CH(Me)Et	H	66 (20)
4	**1c**	*n*-Bu	$CH(Et)_2$	H	86 (64)
5	**1d**	*n*-Bu	$(CH_2)_2$−Ph	H	81 (58)
6	**1e**[c,d]	*t*-Bu	Ph	H	65 (51)
7	**1f**[c]	*n*-Bu	Ph	Ph	90 (58)
8	**1g**	*t*-Bu	*n*-Pent	*n*-Pent	44 (18)

[a] NMR yields (isolated yield after flash chromatography on silica gel). [b] As a 70/30 mixture of two trans stereoisomers. [c] Reaction required 3 equiv of RLi to achieve completion. [d] As a 63/37mixture of two diastereomers.

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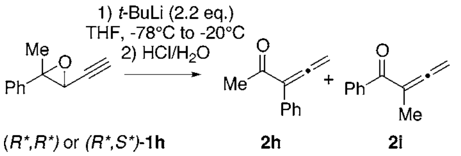
with TBAF. Reaction of these acetylenic oxiranes in our conditions gives, upon hydrolysis, the corresponding allenic ketones in fair to good isolated yields. It should be noted that in most cases, the allenic products were obtained as sufficiently pure crude materials; purification by flash chromatography gave analytically pure materials but, in some cases, in lower yields.

As seen in Table 1, allenic ketones can be obtained from monosubstituted acetylenic oxiranes (entries 1−5) through 1,2-H shift in good yields. In the case of 2,2-disubstituted acetylenic oxiranes, 1,2-Ph shift was also observed (Table 1, entry 7), whereas 1,2-alkyl shift arises in lower yields, accompanied by important side reactions (entry 8). However, 1,2-Me shift (leading to allenic ketone **2i**) was also observed in the case of oxiranes **1h**-(*R**,*S**) and **1h**-(*R**,*R**) (Scheme 5), although 1,2-Ph shift (leading to allenic ketone **2h**) remained the major rearrangement pathway, whatever the stereochemistry of the starting oxirane. All these results allow us to determine the following order of shift ability: 1,2-H shift > 1,2-Ph shift > 1,2-Me shift.

Scheme 5

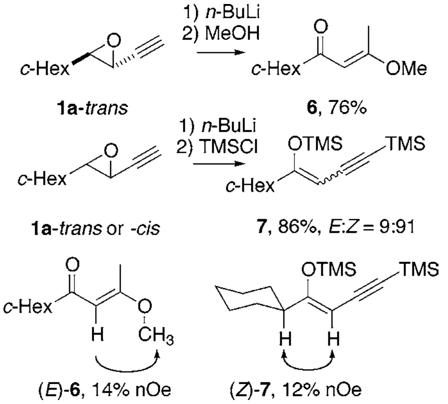


From (*R**,*R**)-**1h**: 68%, **2h**:**2i** = 69:31
From (*R**,*S**)-**1h**: 90%, **2h**:**2i** = 91:9

Having established the scope and the mechanism of this new reaction, we then turned to the chemical behavior of the resulting dilithio ynenolate **5**. As depicted above (Scheme 1), hydrolysis (respectively, deuteriolysis) of the dianion **5** obtained from **1a** afforded allenic ketone **2a** (respectively, D_2-**2a**). In contrast, methanolysis of the reaction mixture gave interestingly methoxyenone **6** in 76% isolated yield as a single isomer (Scheme 6). The latter was shown to be the (*E*)-isomer by NOE experiments and is presumably formed through the stereoselective addition[9] of methanol onto allenic ketone **2a** formed through protonation of **5**.

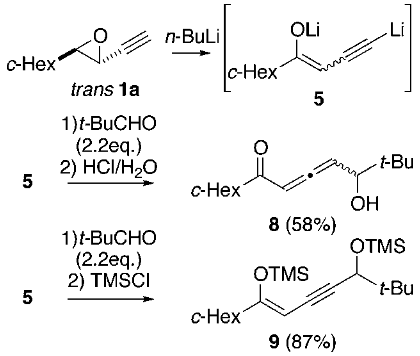
On the other hand, quenching the reaction mixture resulting from the rearrangement step on **1a**-*trans* with TMSCl gave the TMS-enolate **7** as a 91/9 mixture of two stereomers (Scheme 6). The major one was found to be the (*Z*)-isomer by NOE experiments. The same silicon enolate **7** in the same isomeric ratio was obtained from oxirane **1a**-*cis*. This enolate **7** was found to be remarkably and surprisingly stable, as it could be purified by flash chromatography on silica gel.

Scheme 6



As mentioned above, the dilithium *O*,*C*-acetylenic species **5** seems to be the most probable of all the possible lithium dianions. The two anionic species could then show a different reactivity. The reaction of ynenolate **5** derived from oxirane **1a**-*trans* with pivalaldehyde (Scheme 7) gave only the product **8** (as a 50:50 mixture of two diastereoisomers), resulting from the reaction of only one of these two anionic moieties. The bimetallic species **5** apparently reacts only at the acetylenic terminus, even with an excess of pivalaldehyde. On the other hand, quenching the reaction mixture with TMSCl after the reaction with *t*-BuCHO gave the TMS-enolate **9** as a single (presumably *Z*) isomer.

Scheme 7



In conclusion, we have disclosed a general and interesting formation of new dilithium ynenolate species through the unprecedented, double deprotonation of acetylenic oxiranes. The mechanism of this ynenolate formation has been shown to follow a double deprotonation at the acetylenic *and* propargylic positions of the acetylenic oxiranes, followed by 1,2-H or 1,2-Ar shift. The resulting dilithium ynenolates show an interesting reactivity and allow the preparation of various structures. Among them, the formation of allenic ketones in fair to good isolated yields must be underlined. These compounds have been shown to present an interesting

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(8) All compounds **2a**−**i** were fully characterized by their ^{1}H NMR, ^{13}C NMR, and IR spectral data (see Supporting Information).

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reactivity,[10,11] for instance, as Michael acceptors,[12] as Diels−Alder dienophiles,[11] and in furan formation.[9c,13] Various synthetic routes to allenic ketones have been reported in the literature,[10,11,14] and the most largely used preparation involves the reaction of allenylmetals with carbonyl compounds, followed by oxidation of the resulting allenic or homopropargylic alcohols.[11−13,15] Our methodology appears to be competitive with those previously reported in terms of yield and concision. Further results concerning the reactivity of the dilithium ynenolate intermediates will be reported in due course.

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Supporting Information Available: General procedures and spectral data and ^{1}H and ^{13}C NMR spectras for compounds **2a−i** and **6−9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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