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The Use of *trans*-2,3-Divinyl Epoxides as Precursors to Carbonyl Ylides

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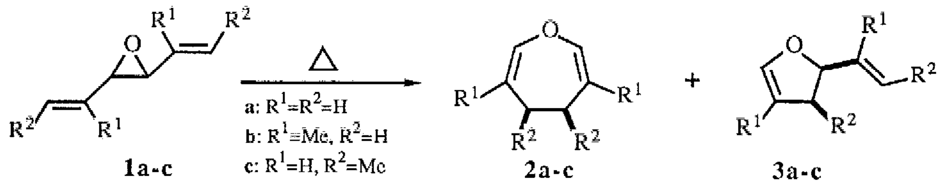
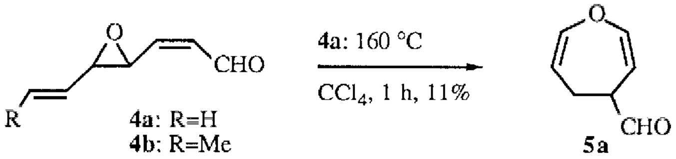
Abstract: *trans*-2,3-Divinyl epoxides have been found to be good substrates for the generation of carbonyl ylides in CCl_4 at 145 °C. These ylides, to a limited extent, undergo isomerization to *cis*-2,3-divinyl epoxides, leading to the isolation of 4,5-dihydrooxepins. Of greater potential usefulness is the finding that these ylides can be efficiently trapped in an intermolecular sense by a dipolarophile, leading to dihydrofurans.

Whereas *trans*-1,2-divinylcyclopropanes oftentimes provide the products from their formal [3,3] sigmatropic rearrangements, 1,4-cycloheptadienes, in synthetically useful yields,[1] the Cope rearrangements of 2,3-divinyl epoxides cleanly provide the corresponding 4,5-dihydrooxepins in good yield only when the stereochemistry of the epoxide is cis. Thermal rearrangements of *trans*-2,3-divinyl epoxides have been reported,[2] but generally lead to a mixture of products. For example, although the rearrangement of epoxide **1a** at 230 °C was originally reported to give only 4,5-dihydrooxepin (**2a**),[2b] it was later determined that heating **1a** at 170-200 °C resulted in a 30:70 mixture of **2a** and dihydrofuran **3a**.[2c] The biradical from homolytic scission of the carbon-carbon bond of the epoxide was proposed as an intermediate in this reaction, but later work with other *trans*-2,3-divinyl epoxides,[2d-g] particularly the rearrangement of epoxide **1c** to give dihydrofuran **3c** as only the cis isomer,[2d-e] provided convincing evidence that the true intermediate is a carbonyl ylide. In the case of epoxides **4a-b**,[2h-i] the aldehydic group would be expected to stabilize by resonance the anionic portion of the carbonyl ylide, and thereby lower the temperature necessary to effect rearrangement.[3] In fact, heating **4a** at 160 °C gave the product from formal [3,3] sigmatropic rearrangement, oxepin **5a**, albeit in only 11% yield, while the more substituted derivative **4b** decomposed upon heating at 130 °C. Herein we report our own investigation of the use of *trans*-divinyl epoxides as carbonyl ylide precursors.

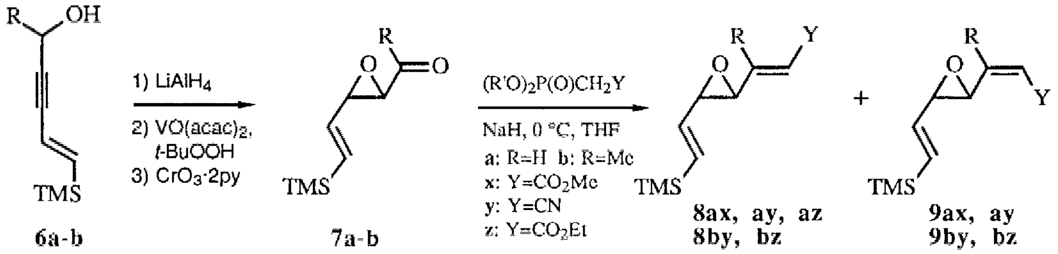


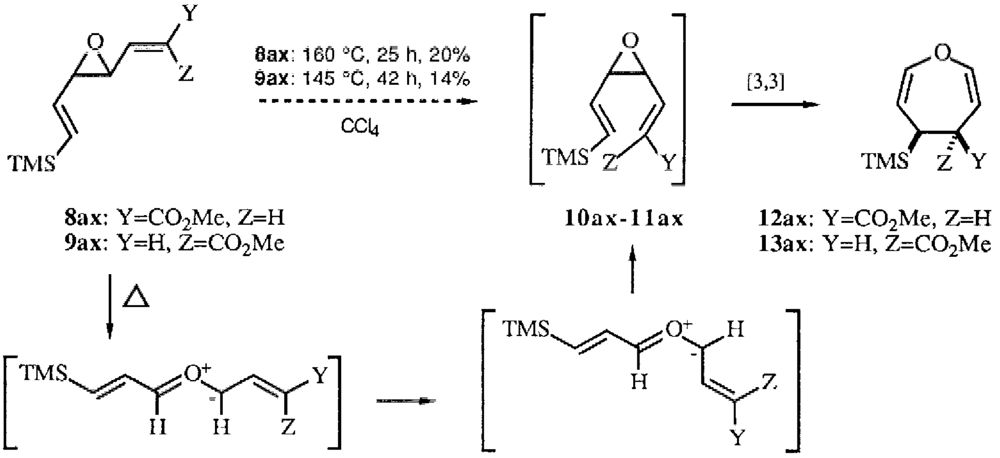
1a-c **2a-c** **3a-c**



4a: R=H
4b: R=Me
5a

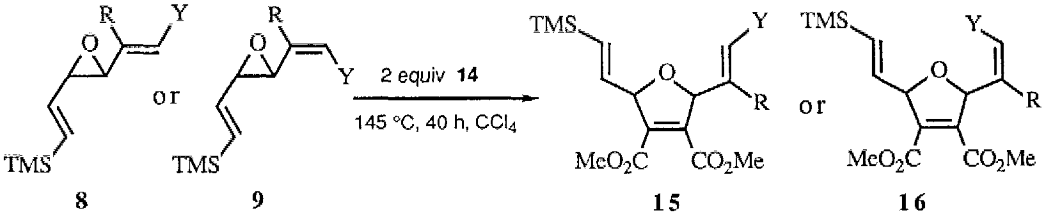
The *trans*-epoxides were prepared from the enynols **6a-b** by a modification of our earlier procedure.[2k] $LiAlH_4$ reduction gave predominantly the *trans*-allylic alcohols, which were converted in two steps to the epoxycarbonyl compounds **7a-b**. Wadsworth-Horner-Emmons olefination then gave the α,β-unsaturated esters and nitriles **8** and **9** as separable mixtures of the *E* and *Z* isomers.[4] In order to test the usefulness of these *trans*-epoxides as precursors to 4,5-dihydrooxepins, the methyl esters **8ax** and **9ax** were each heated in CCl_4 and found to rearrange stereospecifically to the 4,5-dihyrooxepins **12ax** and **13ax**, respectively.[5] This result is consistent with the stereospecific but partial conversion of the *trans*-epoxide to the cis isomer through a carbonyl ylide intermediate that maintains the stereochemical integrity of the olefinic geometry.





Although not a synthetically useful result from the viewpoint of preparing 4,5-dihydrooxepins, these results encouraged us to investigate the potential utility of using the *trans*-epoxides as sources of carbonyl ylides in [3+2] cycloadditions. The generation of such ylides from epoxides substituted with aromatic or electron-withdrawing substituents has precedence,[6a] but most of the synthetic applications of such 1,3-dipoles have made use of carbonyl ylides generated by the intramolecular addition of a carbenoid species to the oxygen atom of a nearby C=O bond.[6b] When *trans*-2,3-divinyl epoxide **8az** was heated in the presence of one equivalent of the dipolarophile dimethyl acetylenedicarboxylate (**14**) (145 °C, 40 h, CCl_4), 2,5-dihydrofuran **15az** was isolated in 30% yield along with a 9% yield of the product from formal Cope rearrangement of **8az**, the *cis*-oxepin **12az**. This result indicated that the carbonyl ylide had a sufficient lifetime to be competitively trapped intermolecularly prior to its consumption either by bond rotation and ring closure to the *cis*-epoxide, or by intervention by some other alternative process. The use of two equivalents of the dipolarophile led to an increase in the yield of the [3+2] cycloadduct and a commensurate decrease in the yield of oxepin **12az**. These latter conditions were adopted as our standard conditions for a preliminary examination of the potential use of this reaction for preparing 2,5-dihydrofurans. The reaction of the methyl ester with the *E* configuration (**8ax**) resulted in a lower yield compared to the ethyl ester **8az**, but the methyl ester with the *Z* configuration (**9ax**) gave a comparable yield to the ethyl ester with the *E* geometry. The higher yield under comparable conditions for the *Z* isomer over the *E* isomer was also observed in the other pairs of substrates that were tested. In the case of the esters **8bz** and **9bz**, this difference is in part a reflection of the greater reactivity under these reaction conditions of the ester with the *Z* stereochemistry (**9bz**), as a significant amount of the (*E*)-α,β-unsaturated ester **8bz** was recovered from its reaction. For the α,β-unsaturated nitriles, not only does having the *Z* configuration raise the yield, but the methyl substituent on the beta carbon of the α,β-unsaturated nitrile also seemed to aid the [3+2] cycloaddition. It should also be noted that in all of these cycloadditions, the stereochemical integrity of both double bonds of the divinyl epoxide were maintained throughout the course of the reaction.[7]

Table. Reaction of *trans*-2,3-Divinyl Epoxides with Dimethyl Acetylenedicarboxylate (14)



Entry	Substrate	R	Y	Product	Yield(%)	Contaminant (%)
1[1]	**8az**	H	CO_2Et	**15az**	30	**12az** (9)
2	**8az**	H	CO_2Et	**15az**	43	**12az** (6)
3	**8ax**	H	CO_2Me	**15ax**	25	**12ax** (2)
4	**9ax**	H	CO_2Me	**16ax**	43	**13ax** (9)
5	**8bz**	Me	CO_2Et	**15bz**	28	**8bz** (28)
6	**9bz**	Me	CO_2Et	**16bz**	41	**9bz** (trace)
7	**8ay**	H	CN	**15ay**	24	
8	**8by**	Me	CN	**15by**	40	
9	**9ay**	H	CN	**16ay**	39	
10	**9by**	Me	CN	**16by**	52	

[1] Only one equivalent of dimethyl acetylenedicarboxylate was used in this experiment.

These cycloadditions appear to be of a general nature, as, for example, heating epoxide **8az** under the standard conditions with the substitution of two equivalents of N-phenymaleimide as the dipolarophile led to a 40% yield of the corresponding [3+2] adduct, along with a 6% yield of oxepin **12az**. The α,β-unsaturated functionality may be important to the success of the generation of the carbonyl ylide, as, for example, heating the methyl ketone **7b** under our adopted standard conditions led to an 80% recovery of the ketone and no discernible product from a [3+2] cycloaddition. This method for generating carbonyl ylides for the purpose of doing [3+2] cycloadditions compliments the use of carbonyl ylides generated from carbenoid addition to an adjacent carbonyl oxygen, and leads to richly functionalized furan derivatives. Studies to optimize the cycloaddition reactions and to make use of the cycloadducts are in progress and will be reported in due course.

Acknowledgements. We thank the Robert A. Welch Foundation for their generous support of this research.

References

1. It should be noted that the *trans*-1,2-divinyl cyclopropanes are considerably less reactive than their cis isomers, and in general are thought to rearrange to the 1,4-cycloheptadienes by isomerization to the *cis*-cyclopropanes through a biradical intermediate. For a lead reference, see: Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930-936 and reference 3 therein.

2. (a) Braun, R. A. *J. Org. Chem.* **1963**, *28*, 1383-1384. (b) Stogryn, E. L.; Gianni, M. H.; Passannante, A. J. *J. Org. Chem.* **1964**, *29*, 1275-1276. (c) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385-401. (d) Pommelet, J.-C.; Manisse, N.; Chuche, J. *C. R. Acad. Sc. Paris* **1970**, *270*, 1894-1897 (e) Pommelet, J. C.; Manisse, N.; Chuche, J. *Tetrahedron* **1972**, *28*, 3929-3941. (f) Crawford, R. J.; Vukow, V.; Tokunaga, H. *Can. J. Chem.* **1973**, *51*, 3718-3725. (g) Vukow, V.; Crawford, R. J. *Can. J. Chem.* **1975**, *53*, 1367-1372. (h) Balci, M.; Sütbeyaz, Y. *Tetrahedron Lett.* **1983**, *24*, 4135-4138. (i) Sütbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312-2317. (j) Hudlicky, T.; Fleming, A.; Lovelace, T. C. *Tetrahedron* **1989**, *45*, 3021-3037. (k) Clark, D. L.; Chou, W.-N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975-3977.

3. It should be noted that the product(s) from the rearrangement of a divinyl epoxide can be temperature dependent. For examples, see references 2f and 2j.

4. For each of the following pairs of olefinic isomers is given the *E/Z* ratio, overall yield, and the phosphonate used for the olefination. **8ax/9ax**, 2:1, 82%, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$; **8ay/9ay**, 2.5:1, 56%, $(EtO)_2P(O)CH_2CN$; **8az**, 75%, $(EtO)_2P(O)CH_2CO_2Et$; **8by/9by**, 3.5:1, 64%, $(EtO)_2P(O)CH_2CN$; **8bz/9bz**, 1:1, 73%, $(EtO)_2P(O)CH_2CO_2Et$.

5. The corresponding *cis*-epoxides **10ax-11ax** are superior substrates for Cope rearrangement. The rearrangements in CCl_4 of both **10ax** to the 4,5-dihydrooxepin **12ax** and **11ax** to **13ax** proceeded in 84% yield (100 °C, 12 h) and in 62% yield (130 °C, 24 h), respectively (Whe-Narn Chou and James B. White, manuscript submitted).

6. (a) For a lead reference, see: Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572-585.
   (b) For a lead reference, see: Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22-28.

7. Although the stereochemistry of the 2,5-dihydrofuran ring was not established in this study, it is presumed to be cis. ^{13}C NMR (50.3 MHz, $CDCl_3$) data reported relative to the center line of $CDCl_3$ as δ 77.0. **15ax**: δ166.4, 163.1, 161.7, 144.4, 141.4, 141.1, 135.8, 133.6, 122.4, 89.7, 84.4, 52.6, 52.5, 51.8, -1.58; **16ax**: δ 165.9, 163.2, 162.2, 145.4, 142.1, 138.7, 136.4, 134.0, 121.6, 88.5, 81.9, 52.5, 52.3, 51.6, -1.52; **15ay**: δ 161.9, 161.3, 150.9, 142.5, 140.4, 136.9, 131.8, 116.8, 101.1, 89.9, 84.0, 52.8, 52.6, -1.61; **16ay**: δ 162.7, 161.4, 149.4, 142.5, 140.8, 135.4, 132.8, 114.7, 102.3, 89.8, 83.4, 52.6, -1.58; **15az**: δ 165.9, 163.0, 161.7, 144.0, 141.2, 135.7, 133.7, 123.0, 89.6, 84.5, 60.6, 52.6, 52.5, 14.2, -1.59; **15by**: δ 162.4, 162.0, 159.5, 141.0, 140.1, 136.2, 134.9, 116.1, 99.9, 89.3, 88.4, 52.7, 52.5, 16.8, -1.61; **16by**: δ 162.5, 161.6, 158.9, 142.0, 140.0, 136.2, 134.3, 115.3, 98.9, 89.4, 85.5, 52.6, 52.5, 18.3, -1.61; **15bz**: δ 166.0, 162.6, 162.5, 153.0, 140.7, 139.6, 136.9, 135.4, 120.3, 90.9, 89.0, 60.0, 52.6, 52.4, 14.4, 14.2, -1.58; **16bz**: δ 165.4, 162.9, 162.4, 153.0, 140.9, 139.0, 137.4, 135.1, 120.4, 88.4, 82.7, 60.2, 52.4, 52.2, 19.7, 14.2, -1.56.

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