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Regioselective MCPBA-Oxidation of Alkenylidenecyclopropanes: A Convenient Synthesis of 2-Methylenecyclobutan-1-ones and Cyclopropyl Keto Esters

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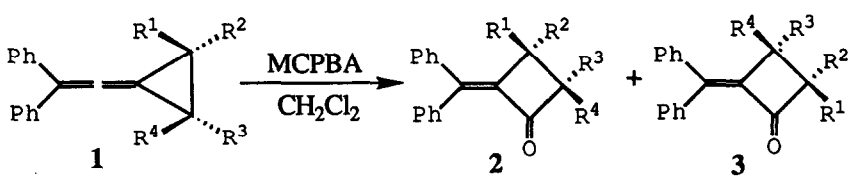
Abstract: *The oxidation of (diphenylethenylidene)cyclopropanes and (dialkylethenylidene)cyclopropanes with m-chloroperbenzoic acid gave respectively 2-(diphenylethylidene)cyclobutan-1-ones and cyclopropyl keto esters with high selectivity.*

2-Alkylidenecyclobutanones are a versatile intermediate in organic synthesis. They can be prepared in most cases by the cycloaddition of ketenes with allenes.[1-4] However, these methodologies have limited utilizations because the substrates required in these reactions are sometimes not easily accessible. Recently, we have reported a convenient method for the preparation of ethenylidenecyclopropanes from 1,1-disubstituted 2,2-dibromocyclopropanes and alkenes.[5] This reaction involves ethenylidenecarbenes as a key intermediate and provides the preparation of ethenylidenecyclopropanes having a wide variety of substitution patterns.

We now report a remarkable regioselectivity in the oxidation of ethenylidenecyclopropanes with m-chloroperbenzoic acid (MCPBA). This reaction provided a convenient method for the preparation of 2-(diphenylmethylene)cyclobutan-1-ones and cyclopropyl keto ester derivatives.



1 2 3

Table. Preparation of 2-Methylenecyclobutanone Derivatives

Alkenylidenecyclopropane		Product(s)	Product ratio[a] 2 : 3	Total yield / %[b]
1a	R^1=R^3=Me, R^2=R^4=H	**2a**	—	50
1b	R^1=R^4=Me, R^2=R^3=H	**2b**	—	69
1c	R^1=R^2=Me, R^3=R^4=H	**2c, 3c**	42 : 58	72
1d	R^1=R^2=R^3=Me, R^4=H	**2d, 3d**	50 : 50	72
1e	R^1=R^2=R^3=R^4=Me	**2e**	—	30
1f	R^1~R^4=-$(CH_2)_4$-, R^2=R^3=H	**2f**	—	89
1g	R^1=OEt, R^2=R^3=R^4=H	**2g**	100 : 0	30
1h	R^1=Me, R^2=Ph, R^3=R^4=H	**2h,3h**	88 : 12	38

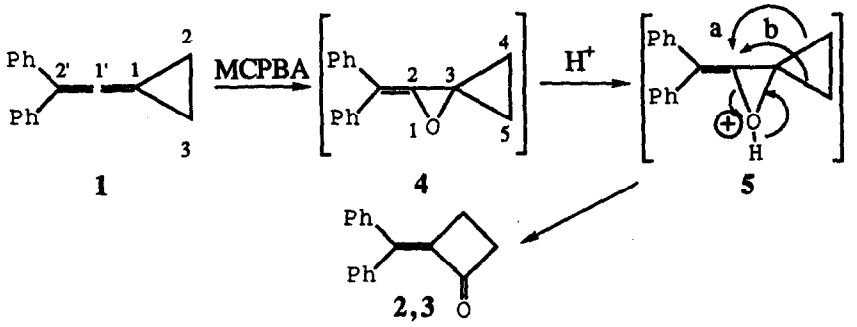
[a] Ratios are determined by 270 MHz ^{1}H NMR spectra.
[b] Isolated yield based on **1** used.

A general procedure is shown by the conversion of trans-2,3-dimethyl-1-(diphenylethenylidene)cyclopropane **1a** into trans-2,3-dimethyl-4-(diphenylmethylene)cyclobutan-1-one **2a**: To a stirred solution of **1a** (1 mmol) in CH_2Cl_2 was added MCPBA (2 mmol) at room temperature. The mixture was further stirred for 24h at the same temperature and concentrated under reduced pressure. Column chromatography of the residue on silica gel with hexane-benzene (1:2) gave **2a** in 50% yield. Similar treatments of (diphenylethenylidene)cyclopropanes **1b-h** gave 2-diphenylmethylenecyclobutan-1-ones **2b-h, 3c-d, 3h**. It should, however, be noted that the MCPBA oxidation of **1c-d** and **1h** gave **2c-d** and **2h**, and also their regioisomers **3c-d** and **3h**. The structures of the products were determined by their spectral properties (^{1}H NMR, ^{13}C NMR, and IR spectra) and elemental analyses.[6]

A striking feature of this reaction is that the stereochemistry of C_2 and C_3 of the cyclopropane ring of **1** was completely retained. Thus, the epoxidation of **1a** and **1b** gave stereospecifically **2a** and **2b**, respectively. However, the regioselectivity in the formation of cyclobutanones depended on the substituents on the cyclopropane ring of **1**.

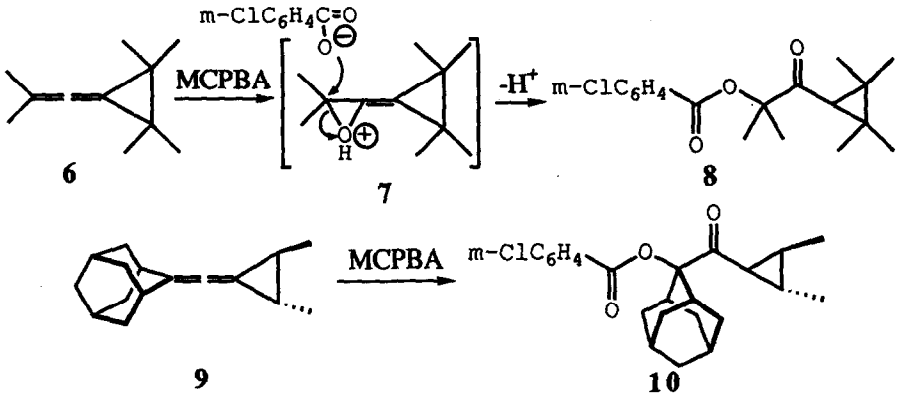
A proposed mechanism of this conversion is shown in Scheme 1. The first step is the epoxidation of **1** with MCPBA to produce 2-(diphenylmethylene)-1-oxaspiro[2.2]pentanes **4**. The acid-promoted rearrangement of **4** gives 2-(diphenylmethylene)cyclobutan-1-ones **2** and **3** via the C_3-C_4 bond migration (path a) and the C_3-C_5 bond migration (path b) respectively. The migratory aptitudes of these two bonds are fundamentally similar to those observed for other carbocation rearrangements.

The rearrangement of this sort has a precedent. Aue and coworkers



Scheme 1.

have reported that the Lewis acid-catalyzed rearrangement of 1-oxaspiro-[2.2]pentanes gives cyclobutanones.[7] However, it has also been reported that the MCPBA oxidation of 1-(2,2-dimethylethenylidene)-2,2,3,3-tetramethylcyclopropane **6** affords the keto ester **8** via the epoxide **7**.[8,9] We also confirmed this rearrangement reaction: Treatment of **6** with MCPBA in CH_2Cl_2 under similar conditions as above gave **8** in 49% yield (scheme 2). We also found that 1-(1-adamantylethenylidene)-trans-2,3-dimethylcyclopropane **9** could be converted into the keto ester **10** in 49% yield in a similar manner with high selectivity (Scheme 2).



Scheme 2.

These results indicate that the regioselectivity in the epoxidation of ethenylidenecyclopropanes strongly depends on substituents on the 2' position of the ethenylidene group of cyclopropanes. When the substituents are alkyl groups as in the cases of **6** and **9**, the electron-rich double bond, the C_1'-C_2' double bond, is oxidized. One the other hand, when the substituents are phenyl group, the epoxidation occurs on the C_1-C_1' double bond in a highly regioselective fashion. This remarkable regioselectivity

in the epoxidation of allenic functionality is, to our knowledge, the first example and may be ascribed to the steric and electronic effects of phenyl group: Note that the phenyl groups at the C_2' position cannot be coplaner with the C_1'-C_2' plane by a steric reason.

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