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Generation of Alkylidene Carbenes from α,β-Epoxy-N-aziridinyl Imines. A New Route to Cyclopentenols

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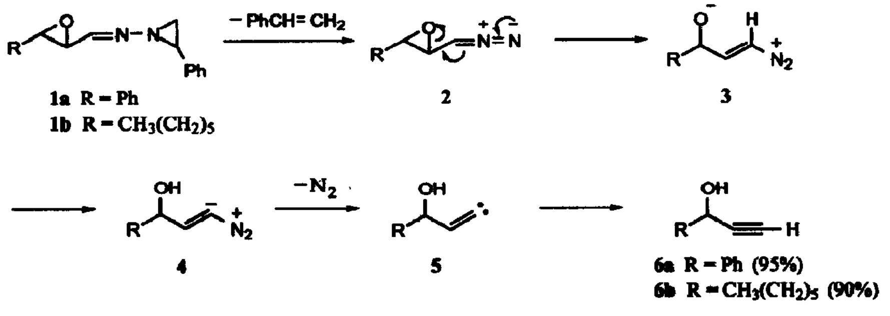
Abstract : Thermal reaction of α,β-epoxy-N-aziridinyl imines in refluxing toluene would initially generate the reactive alkylidene carbenes which underwent intramolecular carbon-hydrogen insertion reactions to afford cyclopentenols.

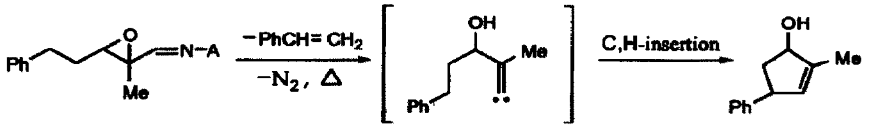
Alkylidene carbenes have received a great deal of recent attention as useful reactive intermediates in organic synthesis[1] and have been known to undergo 1,2-migration,[2] intramolecular 1,5-insertion,[3] and intermolecular insertion.[4] Alkylidene carbenes have been readily generated by base-induced α-elimination of primary vinyl halides or triflates[5] and by nucleophilic β-addition to alkynyliodonium salts and the subsequent reductive cleavage.[6]

Eschenmoser invented a most ingenious as well as synthetically useful reaction related to thermal decomposition of the aziridinyl imines of α,β-epoxy ketones,[7] even though the mechanistic insight has not been completely elucidated. Furthermore, N-aziridinyl imines have been utilized as precursors of both diazoalkanes[8] and carbenes.[9]



Scheme 1

In the course of studies on synthetic utility of N-aziridinyl imines,[10] we have had a chance to examine the thermal reaction of α,β-epoxy-N-aziridinyl imines. When **1a** was refluxed in toluene for 3 h, **6a** was isolated in 95% yield. The possible rationale for this observation is outlined in Scheme 1. It is reasonable to assume that thermal reaction of **1** in refluxing toluene would generate α-hydroxyalkylidene carbene **5** via



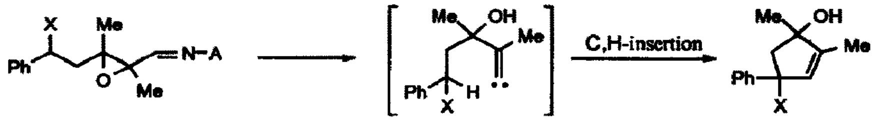
7 A = N-Phenylaziridine **8** **9**

Scheme 2

epoxide ring opening of **2** and subsequent deprotonation in **3** to form **4**, although we do not know whether the deprotonation takes place intramolecularly or intermolecularly. Finally, the well-known 1,2-H shift in **5** would give the α-hydroxy alkyne **6**.[11]

Intramolecular C-H insertion reactions by alkylidene carbenes have been utilized as a powerful tool for the formation of cyclopentenes,[12] although its synthetic usefulness has been somewhat hampered by facile 1,2-H migration to the carbenic carbon and addition to π-bonds. We have examined the possibility of intramolecular C-H insertion reactions of alkylidene carbenes as shown in Scheme 2. When thermolysis of **7** was carried out in refluxing toluene for 8 h, 2-methyl-4-phenyl-2-cyclopenten-1-ol (**9**) was isolated in 73% yield as a 6:4 mixture of the *syn*- and the *anti*- isomer. Apparently, the present reaction proceeded via the intermediate of **8**, in which 1,2-H migration to carbenic carbon can not occur.

Some experimental results are shown in the Table. The generality and versatility of the present method are demonstrated by the formation of not only simple cyclopentenols but also fused bicyclic products (entry 3, 5, 7). Similarly, a spiro bicyclic product is also prepared by using the present method (entry 4). Moreover, the present method is applicable to the formation of the bridged bicylic compounds (entry 6, 8), albeit relatively low yields. In the case of entry 8, it is noteworthy that only one product was isolated, although two different types of 1,5-C,H bonds are present.



10a X = SnBu$_3$
10b X = SiMe$_3$

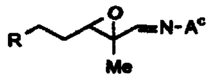
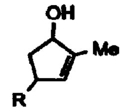
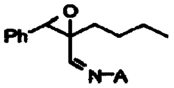
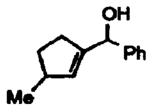
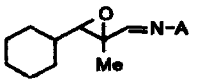
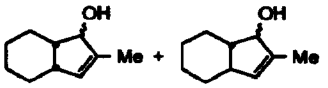
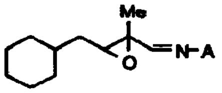
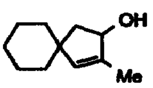
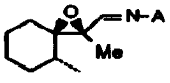
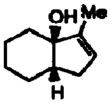
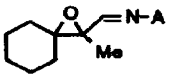
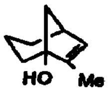
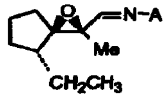
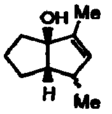
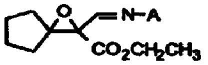
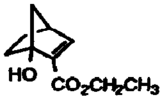
11

12a X = SnBu$_3$ (44%)
12b X = SiMe$_3$ (91%)

Scheme 3

Since we had experienced that 1,n-Bu$_3$Sn transfers (n=5,6) from carbon to oxygen in radical rearrangements were much faster than the corresponding 1,n-hydrogen transfers,[13] our next attention was given to the possibility of intramolecular 1,5-C,SiMe$_3$ and 1,5-C,SnBu$_3$ insertion of alkylidene carbenes. When **10a** was refluxed in toluene for 8 h, only **12a** was isolated in 44% yield as shown in Scheme 3. Apparently, 1,5 C-SnBu$_3$ insertion in **11** did not occur, indicating that C-H insertion reaction of carbenes does not involve a homolytic bond cleavage. A similar result was also obtained with **12b**.

Table. Cyclopentenols via 1,5-C,H-Insertion of α-Hydroxy Alkylidene Carbenes

entry	substrate[a]	product	yield, % (*syn*/*anti*)[b]
1	 R = Ph R = $CH_3(CH_2)_5$		73 (3/2) 71 (3/2)
2			75 (1/1)
3			68 (2/3)[d]
4			70
5			67
6			42
7			62 (4/1)
8			44

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[a] All substrates are a mixture of *syn* and *anti*-isomers and diastereomers. [b] The yield refers to the isolate yield and the number in parenthesis indicates the ratio of diastereomers. [c] A = 2-phenyl aziridinyl group [d] The stereochemistry at the ring junction has been determined by NOE experiment after oxidation of the product.

In conclusion, we have developed a new method for the generation of α-hydroxyalkylidene carbenes from α,β-epoxy-N-aziridinyl imines under mild conditions and demonstrated its synthetic usefulness in the formation of cyclopentenols via intramolecular 1,5-C,H insertion.

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