Application of Fast Radical Rearrangement in the Mechanistic Investigation of Intramolecular C-H Insertion by Rh(II)-Mediated Carbenoids

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Abstract: In order to investigate the reaction mechanism of intramolecular C-H insertion by Rh(II)-mediated carbenoids with trans-(2-phenylcyclopropyl)carbinal radical as the mechanistic probe, diazo compounds 2-(2-phenylcyclopropyl)ethyl diazocetacetate 8a and methyl 2-diazo-3-oxo-6-(2-phenylcyclopropyl)hexanoate 8b have been synthesized. Preliminary investigation of the intramolecular C-H insertion with Rh₂(OAc)₄ as catalyst supports a concerted insertion process.

Keywords: Rh(II)-mediated carbenoids; intramolecular C-H insertion; mechanism.

Intramolecular C-H insertion by Rh(II)-mediated carbenoid has become a reaction of considerable importance in recent years¹. In addition to its numerous synthetic applications², there have been extensive investigations on the mechanism of this reaction³. Although it has been generally believed that the C-H insertion proceeds through a concerted mechanism, the suspicion exists that radical or ionic pairs might be involved in the reaction. For example, Doyle³⁶ and Pirring³⁷ reported that the C-H insertions catalyzed by Rh₂(O₂CCF₃)₄ proceeded with statistical product distribution, which led to the speculation that free carbene might be released from carbenoids. If free carbene is indeed released from carbenoids, the C-H insertion mechanism must follow a radical pair mechanism. However, since the radicals are likely to combine very fast to give a cyclization product, it would be difficult to detect the diradical intermediate.

Scheme 1
In order to address the question about the possible involvement of the diradical intermediate, we reasoned that a fast radical rearrangement might be applied\(^5\). The kinetics of the ring opening of a series of substituted cyclopropylcarbinyl radicals have been systematically studied in recent years\(^5\). The first order rate constants of the ring opening range from 9.4 \(\times\) 10\(^7\) to 5 \(\times\) 10\(^{11}\) at room temperature (Scheme 2). The rate constant of the cyclopropylcarbinyl radical with the phenyl substituent in a three-membered ring is in the order of 10\(^{11}\), which is close to the rate of the fastest possible unimolecular rearrangement\(^6\). This ring opening might be fast enough to compete with the intramolecular diradical combination. Through the analysis of the reaction products, it would be possible to differentiate the concerted mechanism and the diradical process. As shown in Scheme 3, if the C-H insertion proceeds through concerted mechanism, the three-membered ring should remain intact and the insertion should give relatively clean cyclization products. On the other hand, if a discrete diradical intermediate is involved in the reaction, the fast opening of the three-membered ring will compete with the diradical combination and the reaction products in this case will be different from the concerted C-H insertion products, and might be more complicated.

Following the line of reasoning above, we designed diazo compounds 8a and 8b as the precursors for intramolecular C-H insertion. The synthetic procedures for 8a and 8b are outlined in Scheme 4 and Scheme 5. Cu(acac)\(_2\) catalyzed cyclopropanation of styrene with ethyl diazoacetate, followed by hydrolysis, gave trans-2-phenyl-1-cyclopropanecarboxylic acid 15. 15 was then converted to its corresponding diazoketone by standard procedure, followed by Wolff rearrangement\(^7\) and methylation with CH\(_3\)N\(_2\) to give methyl ester 16. Subsequent reduction of 16 provided corresponding alcohol, which
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Following the line of reasoning above, we designed diazo compounds $8a$ and $8b$ as the precursors for intramolecular C-H insertion. The synthetic procedures for $8a$ and $8b$ are outlined in Scheme 4 and Scheme 5. Cu(acac)$_2$ catalyzed cyclopropanation of styrene with ethyl diazoacetate, followed by hydrolysis, gave trans-2-phenyl-1-cyclopropane-carboxylic acid $15$. $15$ was then converted to its corresponding diazoketone by standard procedure, followed by Wolff rearrangement and methylation with CH$_3$N$_2$ to give methyl ester $16$. Subsequent reduction of $16$ provided corresponding alcohol, which
8b, as well as with other catalysts, such as Rh₂(O₂CCF₃)₆ and Rh₂(acac)₆, is currently underway and the results will be reported in due course.

![Scheme 6](image)

Acknowledgments

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References and Notes

6. The theoretical rate constant of fastest possible unimolecular rearrangement, the decay of a transition state to product, is about $6 \times 10^{-12} \text{s}^{-1}$ at $25^\circ \text{C}$.
8. The structure of the cyclization products is assigned to be 23 and 24. Inspection of the $^1H$ NMR spectrum of the mixture of 23 and 24 suggests the acetate group is trans to the cyclopropane moiety, as indicated by the coupling constants between $3-H$ and $4-H$ ($J = 11.0$ Hz, and $J = 10.7$ Hz).

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