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Ring-Opening Addition Reaction of Cyclopropanol Derivatives with Carbenes

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Abstract: Chloro(phenyl)carbene and diphenylcarbene reacted with cyclopropanone hemiacetals, cyclopropanols, and cyclopropanone cyanohydrins to give 4-phenylbutanoic acid derivatives. The mechanism was explained in terms of a homolytic process that the O-H group of cyclopropanols reacted as a formal H donor with carbenes.

General feature of the reaction of carbenes with alcohols is the formation of ethers.[1] Long-lasting discussion on the reaction mechanism of singlet diarylcarbenes with alcohols[2] seems to be terminated recently by Kirmse and Kilian who proved that the initial step is the protonation producing a diarylcarbenium ion.[3] However, protonation seems not always the sole entrance to the reaction of aryl-substituted carbenes with alcohols. We report here a novel type ring-opening addition reaction of carbenes with cyclopropanols which is synthetically intriguing and mechanistically suggesting the involvement of a unique homolytic pathway as well.

A deoxygenated benzene solution (5 ml) of chloro(phenyl)diazirine (**1**) or diphenyl-diazomethane (**2**) (1 mmol) and 1-methoxy-2-phenylcyclopropanol (**3a**) (0.49 mmol)[4] was irradiated with a 300-W high pressure Hg-lamp through a Pyrex filter at 10 °C.[5] After work-up, ring-opened addition product **4h** (48%) from **1** or **4i** (46%) from **2** was isolated. Alkyl-substituted hemiacetal **3b** also gave **4j** and **4k** in the reaction with **1**, and **4l** and **4m** in the reaction with **2**. Simple cyclopropanol **3f** gave **4t** in the reaction with **2** as well. The reaction of **1** with cyclopropanols **3(c, d, e)**[6] bearing an electron withdrawing CN group also gave the ring-opened adduct **4(n, q, s)** though in low yields. In contrast, the reaction of **2** with **3(c, d)** afforded only cyclopropyl ethers **5(p, r)** but not ring-opened adducts **4**. Results are summarized in Table 1.[7]

At first view the formation of **4** seemed to be explained by the protonation mechanism which may be initiated by a singlet carbene **9** at its ground state or singlet carbene **10** at its excited state.[8] However, on the basis of the following experimental evidences (1)-(3) (*vide infra*) the reaction can be more reasonably explained in terms of a homolytic mechanism where a pair of cyclopropyloxy radical and carbene-derived methyl radical constitutes the key intermediate. The evidences which support the free radical profile of the reaction are as follows.

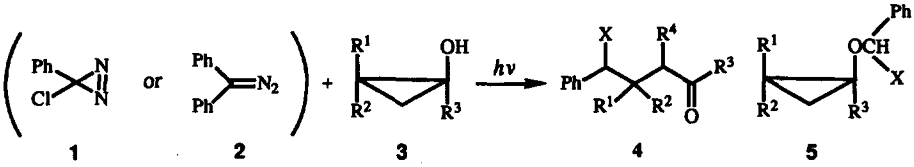


Table 1. Reaction of Cyclopropanols (3) with Chloro(phenyl)carbene (9) and Diphenylcarbene (10)

carbene precursor	solvent[a]	cyclopropanol 3	R^1	R^2	R^3	product 4, 5	X	R^1	R^2	R^3	R^4	yield %[b] 4	yield %[b] 5
1	B	3a	Ph	H	OMe	4h	Cl	Ph	H	OMe	H	48[c]	0
2	B	3a	Ph	H	OMe	4i	Ph	Ph	H	OMe	H	46	0
1	B	3b	$^nC_5$	H	OEt	4j	Cl	$^nC_5$	H	OEt	H	30[d]	0
						4k	Cl	H	H	OEt	$^nC_5$		
2	B	3b	$^nC_5$	H	OEt	4l	Ph	$^nC_5$	H	OEt	H	28[e]	0
						4m	Ph	H	H	OEt	$^nC_5$		
1	E	3c	Ph	Ph	CN	4n	Cl	Ph	Ph	OH	H	18	0
2	B	3c	Ph	Ph	CN	5p	Ph	Ph	Ph	CN	H	0	25
1	E	3d	Ph	Me	CN	4q	Cl	Ph	Me	OMe	H	16	0
2	B	3d	Ph	Me	CN	5r	Ph	Ph	Me	CN	H	0	25
1	B	3e	Ph	H	CN	4s	Cl	Ph	H	CN	H	28	0
2	B	3f	Ph	H	H	4t	Ph	Ph	H	H	H	31	0

[a] B: benzene, E: diethyl ether. [b] Isolated yields determined by column chromatography. [c] Diastereomeric mixture, isomer ratio = 1.0. [d] Isomer ratio 4k : 4j = 2.5. [e] Mixture of two regioisomers, isomer ratio = 1.4, not specified by ^1H NMR

(1) Involvement of a radical pair was demonstrated by the reaction of *d*-labeled 3c-OD (97%-*d*) with 1. Isolated products 4n-*d* (18%) incorporated 89% deuterium (not more than that) on the 4-position. To be noted is that a considerable amount of 8-*d* (dimer of chloro(phenyl)methyl radical 11, 30%) was formed in which a relatively high content of deuterium (70%) was incorporated. Some amount of hydrogen content in 4n-*d* (4n-*h* >11%) and in 8-*d* (8-*h* >30%) show that partial participation of out-of-cage hydrogen abstraction by the carbene also took place to some extent.

(2) When 3,5-di(tertiary butyl)-4-hydroxytoluene (BHT) was added as a radical scavenger in the reaction of 1 with 3a, the yield of 4c was suppressed from 48% to 25% with one equiv BHT, and to 9% with two equivs.

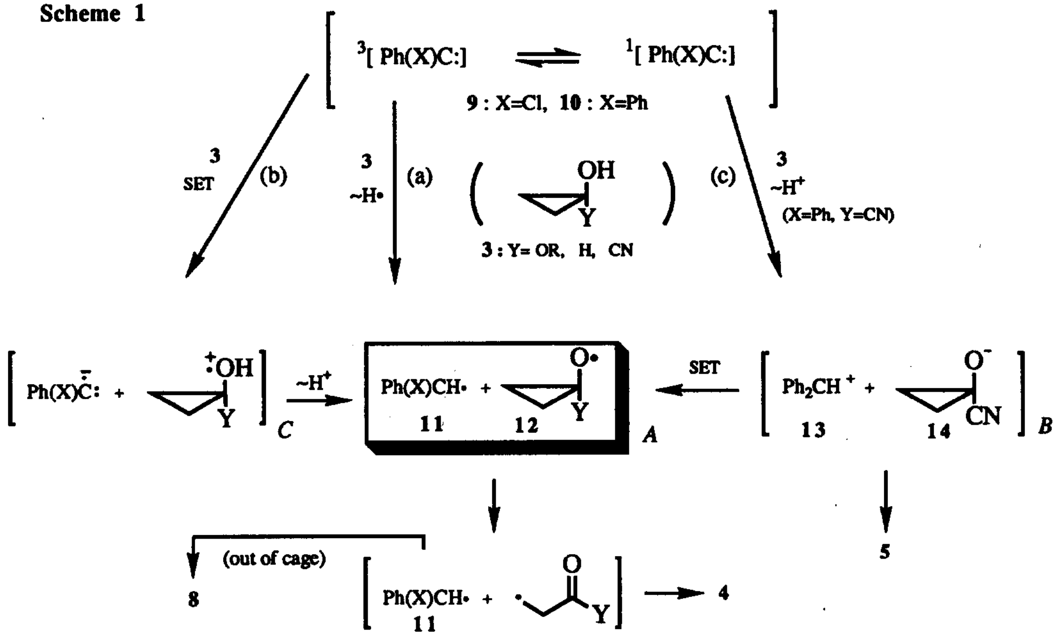
The suppression is also consonant with the free-radical profile of the present reaction. Incomplete suppression may be attributable to a cage effect which favors in-cage coupling of the radical pair even in the presence of BHT.

(3) For comparison, independent reactions of 3a and 3c with bromine under the irradiation with a tungsten lamp were carried out and ring-opened adduct 6 (78%) and 7 (16%) were produced respectively.[9] The formation of 6 and 7 which are similar to those obtained in the reaction with carbenes (*vide ante*) or with molecular oxygen[10] explicitly supports the free-radical mechanism.

$PhCH(Br)CH_2COOCH_3$ (6) $PhCD(Cl)C(Ph)_2CH_2COCN$ (4n-*d*)
$Ph_2C{=}CHCOCN$ (7) $PhCD(Cl){-}CD(Cl)Ph$ (8-*d*)

The reaction behavior of cyclopropanols 3c-e (cyanohydrins) bearing an electron withdrawing CN group changes depending on the nature of carbenes. Thus, while cyclopropanone cyanohydrins 3c-e reacted with carbene 9 to give ring-opened adducts 4, they reacted with carbene 10 to give cyclopropyl ethers 5 as the sole product. Considering both the proton affinity of singlet carbene 10 which is higher than that of ground-state singlet carbene 9 and also the acidity of cyanohydrins which is higher than those of hemiacetals, we can reasonably explain that the cyanohydrin protonates 10 to produce the ion pair of diphenylcarbenium ion 13 and a cyclopropyloxy anion 14, the latter resists ring-opening more than cyclopropyloxy radical 12 does and undergoes rapid coupling with the pairing carbenium ion 13 to form ether 5 in a cage.

Scheme 1



There still remains ambiguity of the initiating step before producing the free radical pair *A* (Scheme 1) for which three routes are presumable: (a) direct hydrogen abstraction from **3** by triplet carbenes **10** at its ground state and **9** at its excited state; (b) single-electron transfer from **3** to carbenes to produce radical-ion pair *C* followed by a proton transfer leading to *A*;[11] (c) proton abstraction by singlet carbenes **10** at its excited state and **9** at its ground state, though usually electrophilic, to produce ion pair *B* followed by single-electron transfer between the paired ions.[12] To summarize, with the preference of route (a) to (b) and (c) as the initiating step of the free radical coupling reaction, we have unveiled the other novel profile of the reaction of carbenes with alcohols.[13]

References and Notes

This paper is dedicated to Professor Harold Hart on the occasion of his 70th birthday.

1. Reviews: (a) Wentrup, C. in *Carbene(oide), Carbine;* Regitz, M., Ed.: Thieme, Stuttgart, 1989; Houben-Weyl, Vol E 19b, Teil 1, pp 824-998. (b) Schoeller, W. W. *Ibid,* pp 47-49. (c) Kirmse, W. *Carbene Chemistry,* 2nd ed.; Academic press: New York, 1971, pp 422-436.
2. (a) Bethell, D.; Newall, A. R.; Whittaker, D. *J. Chem. Soc. B* **1971**, 23-31. (b) Kirmse, W. *Justus Liebigs Ann. Chem.* **1963**,*666*, 9.
3. Kirmse, W.; Killian, J. *J. Am. Chem. Soc.* **1990**, *112*, 6399-6400, and references cited therein.
4. (a) Rousseau, G.; Slougui, N. *Tetrahedron Lett.* **1983**, *24*, 1251-1254. For reviews of cyclopropanols: (b) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, 605-623. (c) Salaun, J. *Chem. Rev.* **1983**, 619-632.
5. Without **1** or **2** cyclopropanols **3** are unchanged under the irradiation conditions.
6. Oku, A.; Yokoyama, T,; Harada, T. *J. Org. Chem.* **1983**, *48*, 5333-5337.
7. Spectroscopic data of compounds **4h**(diastereomeric mixture), **4i**, **4j+k**(mixture), **4l+4m**(mixture), **4n**, **4q**(diastereomeric mixture), **4s**(diastereomeric mixture), **4t**, **5p**, **5r**, **6**, and **7** were consistent with the expected structures. The data are available upon request.
8. The singlet/triplet energy difference $^1S_0$-$^3T_0$ for Ph(Cl)C: has not been reported. Those for Cl_2C: (-13.5 kcal/mol) and Ph_2C: (3.8) are appearing in Houben-Weyl; See ref (1)-(b) pp 9-10 and references cited therein.
9. Under dark conditions the reaction did not take place. In addition, to our knowledge, bromine atom does not abstract proton from an alcohol. It most likely abstracted H atom from the alcohol to trigger its ring-opening
10. Oku, A.; Yokoyama, T.; Harada, T. *Tetrahedron Lett.* **1983**, *24*, 4677-4680.
11. Single electron transfer (SET) mechanism (route *b*) from cyclopropanol to carbene might comprise an alternative path which is consonant to overcome the difference in ground state spin multiplicity. The mechanistic difference lies only in the first step of producing an ion radical pair which finally forms the same product **4**. Cyclopropanone acetals are susceptible to SET due to their high HOMOs (see Aoki, Fujimura, Nakamura, and Kuwajima, *J. Am. Chem. Soc.* **1988**, *110*, 3269) as illustrated by the cycloaddition to TCNE (Schaafsma and Steinberg, *Rec. Trav. Chem. Pays-Bus*, **1966**, *85*, 701) and coupling with quinones (Oku, Abe, and Iwamoto, to be published). In this regard carbenes may react as the acceptor in combination with **3**, though difficult to be proven experimentally.
12. In the reaction of **3c**-OD (*d*>97%) the formation of unnegligeble amount of **4n**-*h* (>11%) as well as **8**-*h* (>30%) seems inconsistent with routes (b) and (c) because **3c**-OH (<3%) was the only one H^+ source.
13. Support by the Grant-in-Aid for Priority Area on Unusual Valency (No. 03233216) is greatly appreciated.

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