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SHORT COMMUNICATION

CYCLOPROPYLMETHOXYCARBENE: A KINETIC LIMIT ON THE 1,2-CARBON MIGRATION

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Cyclopropylmethoxycarbene undergoes ambiphilic–nucleophilic intermolecular reaction with alkenes and methanol, but its intramolecular chemistry (1,2-carbon migration) is suppressed ($k < 3 \times 10^3$ s^{-1}) by the α-methoxy substituent.

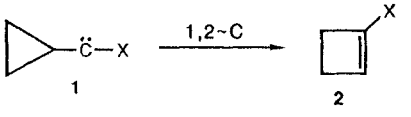
INTRODUCTION

The influence of α-heteroatomic substituents on the kinetics of carbene rearrangements should be profound. For example, high-level *ab inito* calculations on the reaction

$$Me-\ddot{C}-X \xrightarrow{1,2\sim H} CH_2=CHX \qquad (1)$$

predict activation energies of 0·6, 11·5, 19 and 27·2 kcal mol^{-1} (1 kcal = 4·184 kJ), where X = H, Cl, F, or OMe, respectively,[1] so that the 1,2-hydride migration of methylmethoxycarbene[2] should be suppressed relative to alternative, intermolecular reactions. Nevertheless, suppression may not be complete: thermally generated (25 °C) Me—C—OMe appears to give traces of methyl vinyl ether.[2]

In order to examine more closely the dependence of 1,2-carbenic rearrangements on α-heteroatomic substituents, we turned to the cyclopropylcarbene → cyclobutene 1,2-carbon migration:



1 2 (2)

where, using laser flash photolytic (LFP) methodology, we have already measured rate constants and activation parameters for the rearrangements of carbenes **1**-Cl and **1**-F.[3,4] We have now generated cyclopropylmethoxycarbene, **1**-OMe, and found that its intramolecular rearrangement to 1-methoxycyclobutene, **2**-OMe, is indeed suppressed. On the other hand, intermolecular reactions with methanol and alkenes occurred readily. LFP studies not only substantiated the nucleophilic character of **1**-OMe, but also analysis of its reaction with methanol permitted us to assign an upper limit of $k < 3 \times 10^3$ s^{-1} to the 1,2-C migration of **1**-OMe in solution.

RESULTS

Product studies

Cyclopropylmethoxydiazirine, **3**-OMe, was prepared from cyclopropylamidinium chloride.[5] Graham oxidation[6] (aqueous NaOBr, dimethyl sulfoxide) afforded bromodiazirine, **3**-Br (λ_{max}, pentane, 348, 358, 380 nm),[4] which was removed under vacuum at <0.1 mmHg and trapped in dimethylformamide (DMF) at 77 K. Exchange[2,7] with NaOMe (DMF, −30 to −20 °C, 2 h) then provided **3**-OMe (λ_{max}, pentane, 344, 350, 358 nm), which was extracted into pentane or chloroform after an ice–water quench of the reaction mixture. Dried ($CaCl_2$), freshly prepared pentane (or chloroform) solutions of **3**-OMe were used in subsequent experiments. The NMR spectrum of **3**-OMe (δ, $CDCl_3$) revealed cyclopropyl proton multiplets at 0·2–0·3, 0·5–0·6 (2H each) and 0·65–0·75 (1H) and a singlet for OMe at 3.25 (3H).

Diazirine **3**-OMe ($A_{358} \simeq 1·0$) was thermally unstable, decomposing in pentane at 25 °C with $k = 2·1 \times 10^{-3}$ s^{-1}, $\tau_{1/2} \approx 5·5$ min. The products included azine **4**, cyclopropanecarboxyaldehyde, **5**, its

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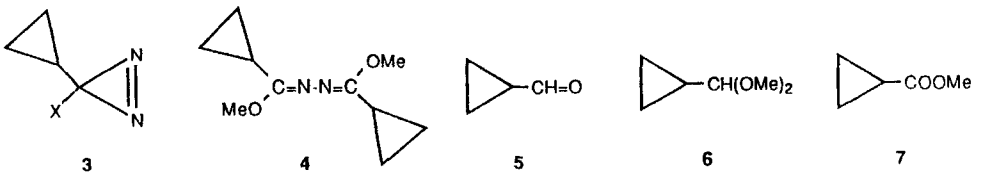
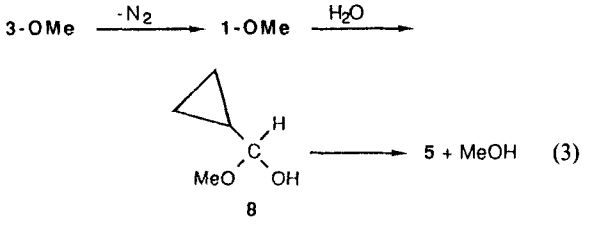


3 4 5 6 7

dimethyl acetal, **6**, and methyl cyclopropanecarboxylate, **7**, in a distribution of 59 : 13 : 16 : 11. The overall yield of azine was 6·5%, based on cyclopropylamidinium salt; assuming 50% yields for the Graham oxidation and diazirine exchange reactions, the decomposition of **3**-OMe to products **4**–**7** must also have proceeded in *ca* 50% yield. Azine **4**, m.p. 93–95 °C, was characterized by NMR and mass spectrometry and elemental analysis, whereas products **5**–**7** were identical [NMR, gas chromatography (GC)] with commercial or independently prepared (**6**)[8] samples.

Aldehyde **5** most likely stems from the capture of carbene **1**-OMe by adventitious water, followed by the loss of methanol from hemiacetal **8**:



(3)

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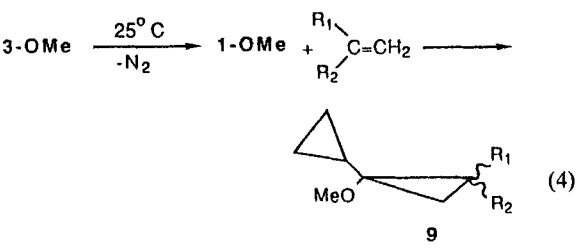
Methanol itself, however, is a powerful carbenaphile (see below), so that it traps **1**-OMe affording acetal **6**. Ester **7** probably represents the reaction of **1**-OMe with oxygen; products analogous to **4**–**7** have been observed in the reaction of Ph—C—OMe.[9]

Significantly, no methoxycyclobutene, **2**-OMe, was observed in thermal or photochemical decompositions of **3**-OMe in either pentane or $CDCl_3$. Authentic **2**-OMe was prepared from cyclobutanone by Gale's procedure;[10] its distinctive NMR spectrum, particularly the vinyl resonance at δ_{CDCl_3} 4.49, made it easy to demonstrate its absence to less than 3% in crude product mixtures. There was also no evidence for the formation of methoxymethylenecyclopropane (δ_{CCl_4} *ca* 6.4[11]), the 1,2 ~ H product of **1**-OMe.

Cyclopropylmethoxycarbene displayed a lively intermolecular chemistry. Thermal decomposition of **3**-OMe in the presence of methanol afforded acetal **6** in >90% yield based on the diazirine. Thermolysis of the diazirine in the presence of excess of alkenes gave the appropriate cyclopropanes, **9** in *ca* 5% yields based on the amidinium salt; cf. equation (4). These yields correspond to *ca* 25% based on diazirine. Additions to the styrenes were accompanied by some azine formation, Cyclopropanes were not observed as significant products in the reactions of **1**-OMe with either trimethylethylene or 2-ethylbutene-1.



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a, $R_1 = R_2$ = Me; **b**, R_1 = CN, R_2 = H
c, R_1 = CN, R_2 = Cl; **d**, R_1 = Ph, R_2 = H
e, R_1 = *p*-MeOPh, R_2 = H; **f**, R_1 = *p*-ClPh, R_2 = H

Except for **9a**, the cyclopropanes were all *syn–anti* isomer mixtures. They were purified by Kugelrohr distillation and/or preparative GC, and characterized by appropriate NMR spectra, elemental analyses and/or exact mass spectrometric measurements.

Kinetic studies

LFP[9] of a freshly prepared pentane solution of **3**-OMe (10 °C, $A_{358} \approx 1{\cdot}0$) at 351 nm, 50–80 mJ, 14 ns, gave rise to a well defined, transient UV absorption (λ_{max} 375 nm) that originated within the time period of the laser pulse. The transient, which we assign to carbene **1**-OMe, decayed with pseudo-first-order kinetics ($k \approx 4 \times 10^4\ s^{-1}$) that were dependent on [**3**-OMe], due to the reaction of the carbene with the diazirine (affording **4**). The UV absorption of **1**-OMe is very similar to that of *trans*-Me—C—OMe (λ_{max} 375 nm);[2] both carbenes also have similar calculated HOMO and LUMO orbital energies (see below).

The LFP UV absorption of **1**-OMe in pentane could be quenched by methanol or alkenes [cf. equation (4)]; trimethylethylene, however, did not quench the carbene on the time scale of the laser experiment ($k < 10^4\ s^{-1}$). Quenching by methanol was effective at very low concentrations; in the range $6 \times 10^{-4} < [MeOH] < 9 \times 10^{-3}$ M, the decay of **1**-OMe was linearly dependent on [MeOH], affording $k \approx 2{\cdot}1 \pm 0{\cdot}8_2 \times 10^8\ l\ mol^{-1}\ s^{-1}$ for the bimolecular rate constant of the **1**-OMe–MeOH reaction. In this concentration range, methanol is most likely reacting as a monomer.[12,13]

When diazirine **3**-OMe ($3{\cdot}6 \times 10^{-5}$ M, relative to an internal cyclohexane standard) was decomposed at

Table 1. Absolute rate constants for reactions of 1-OMe and alkenes[a]

Alkene	$10^{-5}k_2$ (l mol^{-1} s^{-1})[b]
CH_2=CHCN	28 ± 5
CH_2=CClCN	59 ± 2
p-$MeOC_6H_4CH$=CH_2	3·8 ± 0·2
p-MeC_6H_4CH=CH_2	1·7 ± 0·1
C_6H_5CH=CH_2	2·4 ± 0·1
p-ClC_6H_4CH=CH_2	4·1 ± 0·7[c]
m-ClC_6H_4CH=CH_2	1·5 ± 0·4

[a] At 10 °C in pentane.
[b] Errors are average deviations of two determinations except where indicated.
[c] Average of three determinations.

25 °C in a $CDCl_3$ solution that was $7·4 \times 10^{-5}$ M in methanol, NMR analysis indicated a 97% conversion to acetal **6**, with no sign of cyclobutene **2**-OMe. Assuming that the acetal formation (k_ψ) is pseudo-first order, and recalling that $k \approx 2 \times 10^8$ l mol^{-1} s^{-1} for the **1**-OMe–MeOH reaction, k_ψ should be *ca* $1·5 \times 10^4$ s^{-1} under our reaction conditions. We estimate that we could easily detect 20% of cyclobutene **2**-OMe vs acetal **6**, so that the first-order rate constant for **1**-OMe → **2**-OMe cannot exceed $(1/5)k_\psi \approx 3 \times 10^3$ s^{-1} in chloroform at 25 °C.

Quenching of LFP-generated **1**-OMe in pentane could also be accomplished with alkenes, with bimolecular rate constants extracted in the usual manner.[9,14] These results are collected in Table 1.

DISCUSSION

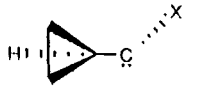
In contrast to the behavior of carbenes **1**-Cl and **1**-F, **1**-OMe does not undergo the intramolecular 1,2-carbon migration reaction in solution; the expected rearrangement product, **2**-OMe, cannot be detected. So uncompetitive is the ring expansion pathway that **1**-OMe preferentially undergoes intermolecular reactions with its diazirine precursor (affording azine **4**), and also with trace amounts of water, methanol or oxygen (yielding products **5**–**7**).

The near quantitative conversion of **1**-OMe to acetal **6** with methanol serves to fix an upper rate constant limit for the (unobserved) **1**-OMe → **2**-OMe rearrangement of *ca* 3×10^3 s^{-1}. This can be compared with rate constants of 9×10^5 and $1·4 \times 10^5$ s^{-1} for the **1**-Cl → **2**-Cl[3a] and **1**-F → **2**-F[4] rearrangements, respectively. Clearly the α-methoxy substituent in carbene **1** effectively suppresses the 1,2 ~ C rearrangement relative to the α-Cl or α-F substituents.

The observed activation energies for the **1**-Cl[3b] and **1**-F[4] rearrangements are 3·0 and 4·2 kcal mol^{-1}, respectively. If the pre-exponential factor for the putative 1,2 ~ C shift of **1**-OMe were as unfavorable as those observed for **1**-Cl and **1**-F (log $A \approx 8·2$–$8·3$ s^{-1}), then, from the maximum rate constant, we can estimate that E_a for **1**-OMe → **2**-OMe must be at least 6·5 kcal mol^{-1}.

The activation energies for 1,2 ~ C shifts in carbenes **1**-X are 4–5 times smaller than the corresponding calculated values for 1,2 ~ H shifts in Me—C—X, but they do fall in the expected order as a function of X, viz., MeO > F > Cl. We would expect E_a(1,2 ~ C) to be smaller than E_a(1,2 ~ H); indeed, the activation energy for **1**-Cl → **2**-Cl has been calculated as *ca* 8·8 kcal mol^{-1},[3a] compared with 11·5 kcal mol^{-1} for Me—C—Cl → vinyl chloride.[1] Nevertheless, there remain sizable (and as yet unexplained) discrepancies between the calculated and (very low) observed activation energies for 1,2 ~ C reactions. Conceivably, heavy atom tunneling might be involved.

The absolute rate constants (Table 1) for the additions of **1**-OMe to various alkenes reveal the ambiphilic–nucleophilic pattern[15] of reactivity that would be expected for a monoalkoxycarbene,[2,9] Geometry-optimized *ab initio* calculations afforded orbital energies (in eV) computed at the HF/4–31G//3G level for the *trans*-**1**-X carbenes (**10**): $\varepsilon_{LU}(p) = 2·01$ (X = Cl), 2·88 (X = F) and 3·97 (X = OMe); $\varepsilon_{HO}(\sigma) = -10·08$ (X = Cl), −10·32 (X = F) and −9·43 (X = OMe) (all *ab initio* calculations made use of the Gaussian 88 series of progams;[16] a detailed description of the methods used in this work can be found in Ref. 17). The pronounced increase in ε_{LU} as X



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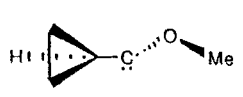

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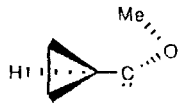

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is changed from Cl to F to OMe is consistent with a change from the predominant electrophilicity of **1**-Cl[18] to the observed ambiphilicity–nucleophilicity of **1**-OMe.

Indeed, computations of the differential orbital energies[15] ($\varepsilon^{LU}_{carbene} - \varepsilon^{HO}_{alkene}$) and ($\varepsilon^{LU}_{alkene} - \varepsilon^{HO}_{carbene}$) for the reactions of **1**-OMe with the alkenes in Table 1 predict that the second or 'nucleophilic' term should be dominant in each carbene–alkene addition reaction. Moreover, the orbital energies of *trans,trans*-**1**-OMe (**11**) and *trans*-Me—C—OMe ($\varepsilon_{LU} = 4·04$ eV, $\varepsilon_{HO} = -9·41$ eV)[2] are nearly identical, so that their philicities should be similar. It is unclear, however, why the nucleophilicity of Me—C—OMe toward α-chloroacrylonitrile is much more strongly expressed[2] than that of **1**-OMe, although

enhanced steric problems are conceivable in additions of **1**-OMe (**11**).

Finally, we note that the *trans*(cyclopropyl), *trans*(methyl) conformer of **1**-OMe (**11**) is the calculated global minimum; the *trans*(cyclopropyl), *cis*(methyl) conformer (**12**) is 2·0 kcal mol^{-1} higher in energy; the remaining local minima, *cis*(cyclopropyl), *trans*(methyl)-**1**-OMe and *cis*(cyclopropyl), *cis*(methyl)-**1**-OMe, are found 7·6 and 19·9 kcal mol^{-1}, respectively, above **11** (these calculations are at the MP2/6–31G*//6–31G* level: cf. Ref. 17).

CONCLUSION

Cyclopropylmethoxycarbene displays ambiphilic–nucleophilic selectively toward alkenes in solution. However, its intramolecular chemistry is effectively suppressed by the α-methoxy carbenic substituent. The absence of 1-methoxycyclobutene, the putative product of a 1,2 ~ C shift, after trapping of the carbene with methanol, permits us to place an upper limit of *ca* 3×10^3 s^{-1} on the rate constant of the 1,2 ~ C rearrangement in solution.

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