Acetoxycarbenes: Modified Oxacarbenes with Enhanced Reactivity

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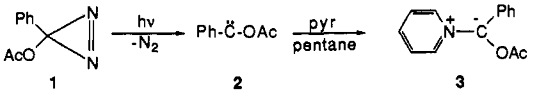
The strongly resonance donating methoxy group stabilizes singlet relative to triplet carbenes,[1] mitigates their reactivity,[2–4] and accentuates their nucleophilic properties.[5–7] Modulation or "tuning" of the electronic properties of the oxa substituent should lead to "designer" oxacarbenes of varied reactivity and synthetic utility. For example, the trifluoroethoxy group, CF_3CH_2O, is a weaker resonance donor (σ_R^+ −0.56)[8–10] than methoxy (σ_R^+ −0.66), and (trifluoroethoxy)carbenes are somewhat more reactive than analogous methoxycarbenes.[10,11]

The acetoxy substituent is of further interest because it is a still weaker donor (σ_R^+ −0.26)[12] than trifluoroethoxy. Indeed, on the basis of substituent constants, acetoxycarbenes should be closer in reactivity to the chlorocarbenes [σ_R^+(Cl) −0.21][9] than to the methoxycarbenes.[13] Acetoxycarbenes, however, are virtually unknown and not easily accessible: the flash vacuum pyrolysis of 5-(acyloxy)-4,6-dioxo-1,3-dioxanes efficiently affords (acyloxy)ketenes and (acyloxy)carbenes, but requires a temperature of 450 °C.[14] The pyrolysis of substituted 2,5-dihydro-1,3,4-oxadiazoles does lead to (e.g.) methylacetoxycarbene, but in low yield.[15]

Now we describe preparations of the first acetoxydiazirines, together with the generation, reactions, and absolute kinetics of the derived acetoxycarbenes. Our studies suggest that acetoxycarbenes are oxacarbenes of enhanced reactivity, in agreement with the foregoing analysis.[13]

Graham reported that the hypochlorite oxidation of acetamidine in the presence of acetate ion produces a mixture of methylchlorodiazirine and methylacetoxydiazirine,[16] but, in our hands, this method of preparation has proved problematical. However, phenylacetoxydiazirine (**1**) can be made readily from phenylbromodiazirine[16] by the diazirine exchange method.[4,17] Thus, 33 mmol of dry tetrabutylammonium acetate was stirred at 25–30 °C for 20 min with phenylbromodiazirine (from the hypobromite oxidation[16] of 38 mmol of benzamidine) in 100 mL of dry DMF. An aqueous pentane workup gave a pentane solution of **1**, which was dried ($CaCl_2$) and chromatographed over silica gel (1:4 CH_2Cl_2/pentane), affording ~45% of phenylacetoxydiazirine.[18] Pentane solutions of **1** were stable for several days in the dark at ambient temperature. Interestingly, 10–20% of *phenyldiazirine* was also formed, presumably by reductive processes akin to those discussed by Creary.[19]

Ylide Formation. Laser flash photolysis (LFP) at 351 nm of diazirine **1** (A_{366} = 0.4) at 25 °C in pentane containing 0.0122–0.0589 M pyridine gave phenylacetoxycarbene (**2**) and thence ylide **3**, λ_{max} 470 nm;[20] eq 1. From the slope of the observed linear dependence of the pseudo-first-order rate constants for the formation of **3** on the concentration of pyridine, we find $k_{ylide} = (3.5 \pm 0.1) \times 10^7$ M^{-1} s^{-1} for the second-order reaction between carbene **2** and pyridine.[21]



1 2 3

(1)

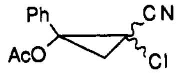
Although the rate of carbene/pyridine ylide formation often approaches diffusion control, this is only characteristic of alkyl, aryl, or halocarbenes.[21] Ylide formation is an electrophilic carbene reaction; the normally nucleophilic[2–6] oxacarbenes are much less reactive. Consider the following absolute rate constants (k_{ylide}, M^{-1} s^{-1}): PhCOMe, 6.9×10^4;[22] $PhCOCH_2CF_3$, 1.8×10^6;[22] PhCOAc, 3.5×10^7; PhCCl, 3.4×10^8.[21] "Tuning" of oxacarbene reactivity is readily apparent in this sequence, and, in its reactivity toward pyridine, oxacarbene **2** is much closer to PhCCl than to PhCOMe.[23]

Rearrangement. Photolysis of a pentane solution of **1** (A_{366} = 0.4) for 1 h at λ > 320 nm destroyed the diazirine and gave >90% of 1-phenyl-1,2-propanedione, **4**, indentified by NMR and GC–MS comparisons to an authentic sample. No azine was observed. A similar yield of **4** was obtained upon thermolysis of **1** in pentane (60 °C, 30 h, sealed tube).

$$\mathrm{Ph\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3}$$

4

5



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The reaction is most simply (but not necessarily most accurately) formulated as a 1,2-acetyl shift of PhCOAc to dione **4**, in accord with prior observations.[14,15] The **2** → **4** rearrangement does not require the high temperature associated with flash vacuum pyrolysis,[14] nor is it a reaction of the diazirine's excited state: it occurs both photolytically and thermally at 60 °C, and it is completely replaced by carbene capture when PhCOAc is generated in (e.g.) acrylonitrile (see below). The (acyloxy)carbene

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(8) Calculated by Professor M. Charton on the scale of ref 9.

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(12) Charton, M. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1989; Vol. 2, Part 1, pp 239–298.

(13) Taking into account the inductive properties (σ_I) of the various substituents,[9,12] and normalizing the σ_R^+ constants to the Ehrenson, Brownlee, and Taft scale (*Prog. Phys. Org. Chem.* **1973**, *10*, 1), we calculate carbene selectivity indices (m_{CXY})[2,4] for representative carbenes, PhCX, as (X=): OMe, 1.34; OCH_2CF_3, 1.22; OAc, 0.76; and Cl, 0.71. Since m_{CXY}(calcd) is directly related to carbenic stability,[3] PhCOAc is predicted to be a relatively unstabilized, reactive oxacarbene.

(14) Brown, R. F. C.; Browne, N. R.; Eastwood, F. W. *Aust. J. Chem.* **1983**, *36*, 2355; **1976**, *29*, 1705. Brown, R. F. C.; Eastwood, F. C.; McMullen, G. L. *J. Chem. Soc., Chem. Commun.* **1975**, 328.

(15) Bekhazi, M.; Warkentin, J. *J. Org. Chem.* **1982**, *47*, 4870.

(16) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(17) Review: Moss, R. A. In *Chemistry of Diazirines*; Liu, M. T. H., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. I, pp 99–109.

(18) UV (pentane): 336, 378 nm. ^1H NMR (δ, $CDCl_3$): 2.18 (s, 3H, CH_3), 6.90–7.00 (m, 2H, Ph), 7.36–7.40 (m, 3H, Ph).

(19) Creary, X.; Sky, A. F.; Phillips, G.; Alonso, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 7584 and earlier papers cited there.

(20) See ref 6 for a description of our LFP installation. Carbene **2** displays a weak absorption at ~310 nm.

(21) The methodology is that of Jackson et al.: Jackson, J. E.; Soundararajan, N.; Platz, M. S.; Liu, M. T. H. *J. Am. Chem. Soc.* **1988**, *110*, 5595. Ylide **3** absorbs at a wavelength similar to that of the analogous PhCCl–pyridine ylide (480 nm).

(22) Moss, R. A.; Jang, E.; Ge, C.-S. Unpublished observations.

(23) Even greater reactivity ($k_{ylide} = 7.8 \times 10^8$ M^{-1} s^{-1}) is displayed by the cyclic relative of **3**, formed via the photolytic rearrangement of benzocyclobutenedione: Boate, D. R.; Johnston, L. J.; Kwong, P. C.; Lee-Ruff, E.; Scaiano, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 8858.

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→ dione rearrangement can also be formally regarded as the reverse of the ketone → oxacarbene photolytic rearrangement.[23,24]

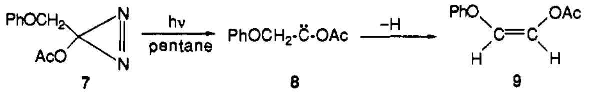
The rate constant for the PhCOAc → **4** rearrangement was found to be $k_{re} = (1.3 \pm 0.2) \times 10^5$ s^{-1} by the pyridine probe method,[21] under conditions under which no azine was formed. The *y* intercept of the linear correlation between the apparent rate constants for ylide formation and pyridine concentration represents the composite rate constant for all those processes that consume carbene **2** in the absence of pyridine. The carbene is cleanly converted to **4** (>90%) in pentane, so that we can equate the *y* intercept with k_{re}. The **2** → **4** rearrangement is a relatively slow process; the lifetime of **2** in pentane is ~7.7 μs. Chemical and theoretical studies are planned to probe the nature of the transition state for this rearrangement.

Addition. Photolysis of diazirine **1** in acrylonitrile or α-chloroacrylonitrile (λ > 320 nm, $A_{366} = 1.2$ or 2.0, 1 h) gave cyclopropanes **5** or **6**, as mixtures of isomers, derived from additions of PhCOAc to the alkenes. Yields exceeded 90%, and product structures were assigned by ^{1}H NMR and high-resolution chemical ionization GC–MS. Absolute rate constants for these additions were determined by the pyridine ylide method,[21] in which **1** ($A_{366} = 1.0$) was subjected to LFP, generating PhCOAc in pentane solutions containing 0.0247 M pyridine and 0.0234–0.642 M acrylonitrile or 0.0250–0.125 M chloroacrylonitrile. Plots of the apparent rate constants for the formation of ylide **3** as a function of alkene concentration were linear (5–7 points, r = 1.000) with slopes that represented k_{addn} for the carbene/alkene reactions.

We found $k_{addn} = (3.54 \pm 0.04) \times 10^6$ or $(5.1 \pm 0.1) \times 10^7$ M^{-1} s^{-1} for the additions of PhCOAc to acrylonitrile or chloroacrylonitrile, respectively, similar in magnitude to k_{addn} for the analogous reactions of PhCOMe (1.7×10^6 or 3.4×10^7 M^{-1} s^{-1})[25] and PhCCl (7.0×10^6 or 2.1×10^8 M^{-1} s^{-1}).[25] Apparently, the reactivities of all three carbenes toward the electrophilic alkenes are roughly similar, although the ordering of k_{addn} is PhCCl > PhCOAc > PhCOMe, as expected from the relative stabilizations of the carbenes that are reflected by their m_{CXY} values.[13] Preliminary experiments indicate that PhCOAc adds well to isobutene, but poorly to trimethylethylene. The carbene's olefinic selectivity requires further study.

Hydride Shift. A particularly clear demonstration of the enhanced reactivity of acetoxycarbenes vs methoxycarbenes was provided by (phenoxymethyl)acetoxycarbene. 3-(Phenoxymethyl)-3-acetoxydiazirine, **7**, was prepared by the reaction of 3-(phenoxymethyl)-3-bromodiazirine[26] with $Bu_4N^+OAc^-$ in DMF for 10 min at 21 °C. Workup and purification, as described for **1**, gave 42% of **7**,[27] accompanied by 2% of the reduced (3-H) (phenoxymethyl)diazirine.

Photolysis of **7** in pentane solution (λ > 320 nm, $A_{328} = 1.0$, 25 °C, 36 h) gave a near quantitative yield of the hydride shift product, *cis*–**9**;[28,29] cf. eq 2.



(2)

A substantial portion of **9** must have arisen from (phenoxymethyl)-acetoxycarbene, **8**, because photolyses of **7** ($A_{328} = 0.8$) in pentane containing 1.87–6.24 × 10^{-3} M pyridine gave rise to strong ylide absorptions at 470 nm. From the slope and intercept of the linear correlation (r = 0.997 for 8 points) between the rate constants for ylide growth and pyridine concentration,[21] we derived $k_{ylide} = (1.03 \pm 0.06) \times 10^9$ M^{-1} s^{-1} and $k_{\sim H} = (4.1 \pm 0.3) \times 10^6$ s^{-1}.

Importantly, although neither $PhOCH_2COMe$ nor $PhOCH_2COCH_2CF_3$ (photolytically generated from the diazirines at 0–20 °C in pentane) gives any hydride shift product,[10] $PhOCH_2COAc$ affords this product quantitatively, with a rate constant that is not very much smaller than those of $PhOCH_2CF$ (1.3×10^7 s^{-1})[26] or $PhOCH_2CCl$ (3.6×10^7 s^{-1}).[26] Presumably, the rapidity of the 1,2-H shift of **8** precludes an alternative but slower 1,2-acetyl shift.

We conclude that acetoxycarbenes are indeed oxacarbenes of unusual reactivity; continuing mechanistic and synthetic studies are in progress.

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(26) Moss, R. A.; Ho, G.-J.; Liu, W. *J. Am. Chem. Soc.* **1992**, *114*, 959.

(27) UV (pentane): 328, 340 (sh) nm. ^{1}H NMR (δ, $CDCl_3$): 2.05 (s, 3H, CH_3), 4.41 (s, 2H, OCH_2), 6.88 (d, J = 7.8 Hz, 2H, *o*-Ph), 6.99 (t, J = 7.4 Hz, 1H, *p*-Ph), 7.29 (*t*, 7.8 Hz, 2H, *m*-Ph).

(28) ^{1}H NMR (δ, $CDCl_3$): 2.22 (s, 3H, CH_3), 6.11 (d, J = 3.7 Hz, 1H, =CH), 6.87 (d, J = 3.7 Hz, 1H, =CH), 7.00–7.35 (m, 5H, Ph). GC–MS, M^+ at *m/e* 178. Anal. (C,H).

(29) A similar preference for (*Z*)-alkene products from the 1,2-H shifts of $PhOCH_2CX$ is also seen with X = F or Cl.[26] See the discussion by Tomioka et al.: Tomioka, H.; Sugiura, T.; Masumoto, Y.; Izawa, Y.; Inagaki, S.; Iwase, K. *J. Chem. Soc., Chem. Commun.* **1986**, 693.