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SHORT COMMUNICATION

TUNING INTRAMOLECULAR CARBENIC INSERTIONS

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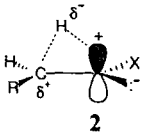
The 1,2-carbenic hydride shift of neopentylmethoxycarbene was suppressed by the methoxy substituent. Thermally activated hydride shifts were observed with phenoxymethylmethoxycarbene and phenoxymethyltrifluoroethoxycarbene, where appropriate potentiating substituents were introduced at both the migration origin and the migration terminus. Similarly, the 1,3-CH insertion reaction of *tert*-butylfluorocarbene could be induced by thermal activation.

INTRODUCTION

The 1,2-C—H insertion (1,2-hydride shift) is a fundamental and ubiquitous intramolecular reaction of singlet alkylcarbenes[1] [equation (1)]:

$$\underset{\mathbf{1}}{RCH_2-\ddot{C}-X} \xrightarrow{1,2-H} RCH{=}CHX \qquad (1)$$

Moreover, the 1,2-H rate constant can be adjusted or 'tuned' by appropriate selection of the 'spectator' substituent, X, in carbene **1**: hydride migrates to the vacant carbenic p-orbital (cf. transition state **2**) so that electron donation by X decreases the vacancy (electrophilicity) of p, increases the activation energy and slows the hydride shift. This theoretical feature of the reaction was well delineated by Evenseck and Houk,[2] who calculated



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$Me_3CCH_2-\ddot{C}-X$ **3-X** (X = F, Cl, OMe) $PhOCH_2-\ddot{C}-X$ **4-X** (X = F, Cl, OMe)

increasing 1,2-H activation energies for CH_3-C-X as a function of the increasing electron-donating ability (σ_R^0) of X (X, E_a in kcal mol^{-1}): H, 0·6; Cl, 11·5; F, 19; *trans*-OMe, 27 (1 kcal = 4·183 kJ). An implicit prediction here is that, at ambient temperature, the 1,2-H shift of alkylalkoxycarbenes will be kinetically 'turned off' relative to alternative carbenic reactions.

The calculations have been at least qualitatively mirrored by experiment. For example, the structural mutation of CH_3-C-CH_3[3] to CH_3-C-Cl[4] is accompanied by a decrease in k_{re} (the rate constant for the 1,2-H shift) from *ca* 5×10^7 to *ca* 1×10^6–3×10^6 s^{-1} (hydrocarbon solvent, 22–25 °C; the statistically collected rate constant ratio is 8–25 : 1). Similarly, in the neopentylhalocarbene series, **3**, changing X from Cl to F decreases k_{re} from $1{\cdot}4\times10^7$ to $2{\cdot}6\times10^6$ s^{-1} (pentane or isooctane, 20 °C).[5]

Inspection of the charge distribution in the 1,2-H transition state, **2**, suggests that the activation energy and therefore the rate constant for 1,2-H can be electronically tuned by substituents at either the migration origin or the migration terminus. The former effect has also been observed,[3,4] and is well illustrated in the phenoxymethylhalocarbene series **4-X**.[5] There, electron donation by PhO mitigates the partial positive charge that develops at the migration origin, accelerating 1,2-H; k_{re} increases from 1×10^6–3×10^6 s^{-1} for CH_3-C-Cl[4] to *ca* 1×10^8 s^{-1} for $PhOCH_2-C-Cl$.[5]

In this paper, we primarily focus on tuning effects with alkoxy substituents. We demonstrate that although 1,2-H migration is indeed shut off by a carbenic alkoxy substituent, it can be restored by a combination of electronic tuning and thermal activation. We also briefly discuss the thermal activation of a substituent-inhibited 1,3-CH carbenic insertion reaction.

RESULTS AND DISCUSSION

The literature demonstrates the difficulty associated with 1,2-H migration in alkylalkoxycarbenes. Thus,

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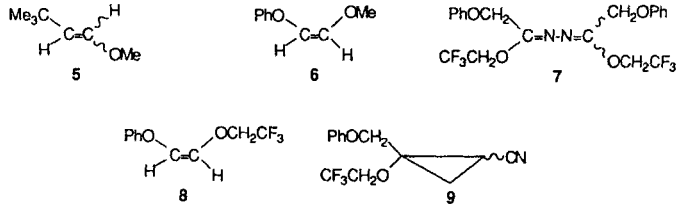
CH_3—C—OCH_3 gave only *ca* 8% of methyl vinyl ether of uncertain origin (25 °C, pentane)[6] and, although a glucose-derived glycosylidene carbene was reported to afford a 1,2-H product as a major component,[7a] further study limited its formation to *ca* 5%.[7b]

In keeping with these observations, photolysis ($\lambda > 320$ nm, pentane, 0 °C) or thermolysis (decalin, 95 °C) of neopentylmethoxydiazirine [λ_{max} 340 nm, pentane; prepared by an exchange reaction of the corresponding bromodiazirine[5] with NaOMe in DMF (−30 °C, 30 min)] (for examples, see Refs 6 and 8) afforded complex product mixtures, presumably via neopentylmethoxycarbene, **3**-OMe. However, careful searches by ^{1}H NMR and GC–MS gave no evidence for the formation of the 1,2-H shift product, **5**. Thus, assuming that alternative carbene reactions are not especially stimulated, the series of carbenes **3**, X = Cl, F, OMe, conforms to expectations,[2] with k_{re} decreasing[5] until, with X = OMe, the 1,2-H migration is no longer competitive (i.e. $k_{re} \leqslant 10^4$ s^{-1}; in our experience, $k_{re} \approx 10^4$–10^5 s^{-1} leads to significant rearrangement product).

5·67 and 5·79 (AB, J = 3·4 Hz, 2H, *cis*-CH=CH), whereas *trans*-**6** exhibited 3·60 (s, 3H, OCH_3), 6·37 and 6·72 (AB, J = 10·4 Hz, 2H, *trans*-CH=CH). Ph multiplets were observed for both isomers at δ 6·9–7·4.

Further tuning of carbene **4**-OMe was achieved by modifying the carbenic methoxy substituent at the migration terminus, mitigating its hydride shift-inhibiting, electron-donating properties by attaching a trifluoromethyl group. Thus, the trifluoroethoxy group is a less effective electron donor than the methoxy group because of the opposed F_3C inductive effect. Indeed, on a scale where σ_R^+(MeO) = −0·66, σ_R^+(F_3CCH_2O) is calculated[9] as −0·56.

3-Phenoxymethyl-3-trifluoroethoxydiazirine [λ_{max} (pentane) = 336 nm] was prepared by diazirine exchange[8] of 3-phenoxymethyl-3-bromodiazirine[5] with $NaOCH_2CF_3$ (DMF, −10 °C, 1 h). Photolysis (0 °C, $\lambda > 320$ nm) or thermolysis (20 °C) of this diazirine (A_{336} = 1·0) in pentane gave only azine **7**, m.p. 94–95 °C, identified by ^{1}H, ^{19}F and ^{13}C NMR, MS and elemental analysis; 1,2-H alkene **8** (see below) was absent by GC or NMR examination. Again, however,



Can the 1,2-H migration, turned off by the carbenic methoxy substituent, be restored? We first introduced the C—H bond-weakening, electron-releasing, hydride shift-stimulating phenoxy substituent[5] at the migration origin.[3,4] Photolysis or thermolysis of phenoxymethylmethoxydiazirine (A_{340} = 1·0 in pentane, 20 °C, prepared in the same manner as neopentylmethoxydiazirine) presumably afforded carbene **4**-OMe, but the 1,2-H shift product, **6**, could not be detected by NMR or GC–MS in the complex mixture of more than 10 products. On the other hand, thermal activation (thermolysis of the diazirine at 95 °C in isooctane) produced a 17% yield of **6** within the still complex product mixture.

Alkene **6** was identical with an independently prepared sample: α-chloroacetaldehyde dimethyl acetal was converted into α-phenoxyacetaldehyde dimethyl acetal (NaOPh, DMF, 100 °C, 24 h, 83%), and the latter was heated with basic alumina (150 °C, 7 h, N_2 stream) to distil out 8% of **6** (*cis*/*trans* = 1·6). The alkenes were purified by GC and characterized by appropriate ^{1}H and ^{13}C NMR, GC–MS (M^+ at m/z 150), and elemental analysis. The ^{1}H NMR of *cis*-**6** (δ, $CDCl_3$) featured absorptions at 3·71 (s, 3H, OCH_3),

thermal activation by rapid injection of an isooctane–diazirine solution into isooctane at 95 °C afforded 52% of the 1,2-H product, *cis*-**8**, via phenoxymethyltrifluoroethoxycarbene, **4**-OCH_2CF_3. Also formed was 14% of azine **7**. Similarly, pyrolysis of the diazirine on a hot glass surface at 95 °C gave 26% of alkene **8** and 37% of azine **7**.

The alkene and azine were separated by column chromatography on silica gel (1 : 8 CH_2Cl_2–pentane) and the alkene was further purified by preparative GC (SE-30, 110 °C). It was characterized by ^{1}H, ^{19}F and ^{13}C NMR, MS (M^+ at m/z 218) and elemental analysis. In particular, the ^{1}H NMR of **8** (δ, $CDCl_3$) revealed absorptions at 4·20 (q, J_{HF} = 8·4 Hz, 2H, OCH_2CF_3), 5·78 and 5·90 (AB, J = 3·5 Hz, 2H, *cis*-CH=CH) and 7·0–7·4 (m, 5H, Ph). The ^{19}F NMR spectrum ($CDCl_3$) featured the CF_3 triplet (J_{FH} = 8·4 Hz) 74·8 ppm upfield from $CFCl_3$. The preferential formation of (*Z*)-alkenes **8** and **6** in these 1,2-H carbene rearrangements is precedented.[5,10]

Acetonitrile is known to enhance k_{re}, relative to pentane solvent, by stabilizing the charge-polarized transition state **2**.[3,11] Indeed, although **8** was not observed when 3-phenoxymethyl-3-trifluoroethoxy-

diazirine was decomposed at 20 °C in pentane (see above), analogous thermal or photochemical decompositions of the diazirine in acetonitrile afforded 10% of alkene **8** in addition to 66% of azine **7**.

When similarly decomposed in pure acrylonitrile, the diazirine afforded carbene **4**-OCH_2CF_3 which was quantitatively captured, affording isomeric cyclopropanes **9**. These were isolated by preparative GC in a 1·4 : 1 isomer ratio and characterized by appropriate ^1H, ^{19}F NMR, MS and elemental analysis. In contrast, with 0·013 M acrylonitrile in acetonitrile solution, the intermolecular addition of **4**-OCH_2CF_3 to acrylonitrile was competitive with 1,2-H rearrangement; on either photochemical or thermal generation of the carbene, we observed an addition/rearrangement product ratio (**9**/**8**) of 2·3.

Kinetics

In pentane, where the 1,2-H migration of **4**-OCH_2CF_3 is *not* competitive with addition, laser flash photolysis,[5] using the pyridine ylide method of visualization,[12] gave $k_{ad} = 6{\cdot}3 \pm 0{\cdot}3 \times 10^7$ l mol^{-1} s^{-1} for the addition of **4**-OCH_2CF_3 to acrylonitrile ([CH_2=CHCN] ranged from 0·0120 to 0·147 M, [pyr] = 2×10^{-3} M). In acetonitrile, we could not determine k_{ad} because the pyridine ylide of **4**-OCH_2CF_3 was very unstable. However, taking k_{ad} (MeCN) as no more than half of k_{ad} (pentane),[13] and recalling that $k_{ad}/k_{re} = 2{\cdot}3$ with 0·013 M acrylonitrile in MeCN, we can estimate $k_{re} \approx 2 \times 10^5$ s^{-1} for **4**-OCH_2CF_3 in acetonitrile. Further, k_{re} should be at least an order of magnitude lower in the non-polar solvent pentane (i.e. $k_{re} \approx 10^4$ s^{-1}) than in acetonitrile,[11] so that, as observed, rearrangement becomes non-competitive with alternative carbenic reactions at ambient temperature.

Allowing for the combined stimulating effect of the PhO substituent, and the decreased inhibiting ability of the OCH_2CF_3 substituent on k_{re} for **4**-OCH_2CF_3, we speculate that k_{re} for a fully 'stripped-down' alkylalkoxycarbene such as CH_3—C—OCH_3 could be as low as *ca* 10^3 s^{-1} in pentane at 25 °C. This estimate is based on the lack of rearrangement for **4**-OCH_2CF_3 at 25 °C ($k_{re} < 10^4$ s^{-1}) and represents a statistically corrected 25,000-fold methoxy-induced diminution of k_{re}, relative to the 1,2-H shift of dimethylcarbene.[3] Thus, kinetic and product studies support the existence of significant activation barriers to 1,2-H rearrangements in alkylalkoxycarbenes,[2] and accord with our expectation that such barriers can be surmounted by an appropriate blend of carbene structural design and thermal activation.

Finally, we note that thermal activation can also be effective in 1,3-CH carbene insertion reactions. For example, photolysis of 3-chloro-3-*tert*-butyldiazirine (**10**-Cl) in $CDCl_3$ at 20 °C gave Me_3C—C—Cl, which mainly afforded the 1,3-insertion product **11**-Cl, together with some of the 1,2-Me migration product, **12**-Cl.[14]

Now, we have prepared diazirine **10**-F [λ_{max} = 344, 362 nm (pentane)] by the diazirine exchange reaction[5,15] of bromodiazirine **10**-Br with Bu_4N^+ F^- (25 °C, DMF, 60 h), where **10**-Br was obtained by the hypobromite oxidation[16] of *tert*-butylamidine hydrochloride. Photolysis ($\lambda > 320$ nm) of $2{\cdot}7 \times 10^{-2}$–$5{\cdot}4 \times 10^{-2}$ M decane solutions of 3-fluoro-3-*tert*-butyldiazirine at 25 °C gave <1% of *tert*-butylfluorocarbene insertion product **11**-F, whereas 75% of the appropriate azine was obtained. This suggests that substitution of F for Cl in Me_3C—C—X raises the activation energy and slows the 1,3-CH insertion enough to shut off this reaction channel relative to an azine-forming intermolecular carbene–diazirine reaction.

In contrast, thermolysis of $5{\cdot}4 \times 10^{-2}$ M **10**-F in decane (145 °C, 6 h, sealed tube) gave 23–25% of insertion product **11**-F, together with 63–66% of the azine. Authentic **11**-F was prepared in 64% yield by the Bu_3SnH reduction[17] of 1-bromo-1-fluoro-2,2-dimethylcyclopropane, with the latter obtained (52%) from the phase transfer-catalysed addition of bromofluorocarbene to isobutene.[18] Cyclopropane **11**-F[19] was characterized by ^1H and ^{19}F NMR spectroscopy and GC–MS.

As with the 1,2-H shifts of carbenes **4**-OMe and **4**-OCH_2CF_3, so too with the 1,3-CH insertion reaction of Me_3C—C—F thermal activation serves to reopen a reaction channel that is otherwise suppressed at ambient temperature.

CONCLUSIONS

Substitution of a methoxy group at the carbenic center of an alkylcarbene suppresses the characteristic 1,2-H rearrangement. This reaction can be restored by the substitution of an electron-donating phenoxy group at the migration origin and by mitigating the electron-donor properties of the methoxy group at the carbenic center (migration terminus) by converting it into a trifluoroethoxy substituent. In these latter instances, restoration of the 1,2-H reaction still requires thermal activation. Similarly, the 1,3-CH insertion reaction of *tert*-butylfluorocarbene, absent at ambient temperature

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because of resonance electron donation from the fluorine substituent, can also be restored by thermal activation.

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