ORGANIC LETTERS
2011
Vol. 13, No. 17
4752–4754

Pentafluorophenylhalocarbenes

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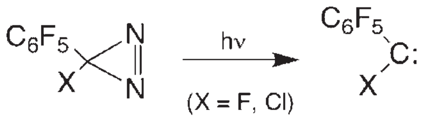
Received July 20, 2011

ABSTRACT



Pentafluorophenylchlorocarbene and pentafluorophenylfluorocarbene are highly reactive species and effective carriers of fluorine labels via addition to alkenes and insertion into C−H bonds.

Fluorine substituents often modify the biological properties of organic molecules.[1,2] Fluorinated reactive intermediates, such as carbenes[1,3,4] or nitrenes,[5] can serve as *carriers* of fluorine into new molecular constructs. However, direct substitution of fluorine on a carbenic carbon stabilizes the carbene and reduces its reactivity;[3,6] carbenes that bear *fluorinated substituents* will be more reactive.

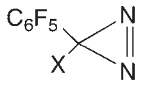
Among candidate substituents, the trifluoromethyl and pentafluorophenyl groups are readily accessible. Trifluoromethyl-substituted carbenes have been extensively examined,[1] but pentafluorophenylcarbenes have received only limited attention. Parent pentafluorophenylcarbene (**1**) is a ground state triplet species which reacts rapidly via its nearby singlet state with a variety of substrates; kinetic data have been reported, but not product characterization.[7]

$C_6F_5-\ddot{C}-H$ **1**

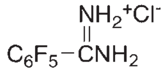
$C_6F_5-\ddot{C}-X$ **2** (X = Cl) **3** (X = F)

Here, we describe reactions of pentafluorophenylchlorocarbene (**2**, PFPCCl) and pentafluorophenylfluorocarbene (**3**, PFPCF) with alkenes and adamantane; products are characterized, and several absolute rate constants are also reported. Singlet ground state carbenes **2** and **3** (see below) are very reactive and should permit the preparation of many pentafluorophenyl-labeled derivatives.

Immediate precursors to carbenes **2** and **3** are the corresponding diazirines, **4a** and **4b**. Diazirine **4a** was prepared by Graham hypochlorite oxidation of pentafluorobenzamidine (**5**) and characterized spectroscopically.[8] In particular, the UV spectrum of **4a** in pentane featured maxima at 326, 333, and 342 nm.[8]



4
a, X = Cl
b, X = F
c, X = Br



$C_6F_5-C(=NH_2^+Cl^-)NH_2$

5

Pentafluorophenylfluorodiazirine **4b** was prepared as illustrated in Scheme 1. Here, the key reactions were Graham hypobromite oxidation[9] of **5** to

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[1] Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803.

[2] Banks, R. E., Smart, B. E., Tatlow, J. C., Eds. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994 (especially Chapters 23−26).

[3] Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585.

[4] (a) Moss, R. A.; Ge, C.-S. *J. Fluorine Chem.* **1995**, *73*, 101. (b) Ge, C.-S.; Jefferson, E. A.; Moss, R. A. *Tetrahedron Lett.* **1993**, *34*, 7549.

[5] (a) Poe, R.; Schnapp, K.; Young, M. J. T.; Grayzar, J.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 5054. (b) Zhai, H; Platz, M. S. *J. Phys. Org. Chem.* **1997**, *10*, 22.

[6] (a) Moss, R. A.; Mallon, C. B.; Ho, C.-T. *J. Am. Chem. Soc.* **1977**, *99*, 4105. (b) Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770. (c) Moss, R. A.; Wang, L.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2009**, *131*, 2128.

[7] Admasu, A.; Gudmundsdottir, A.; Platz, M. S. *J. Phys. Chem. A* **1997**, *101*, 3832.

[8] Wang, L.; Moss, R. A.; Krogh-Jespersen, K. *J. Phys. Chem. A* **2011**, *115*, 8113.

[9] Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

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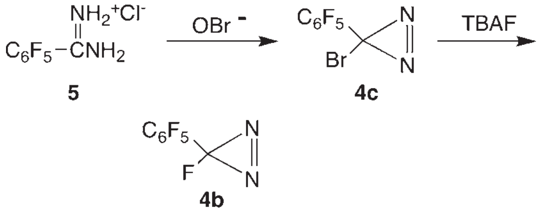
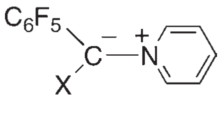
Scheme 1. Preparation of Pentafluorophenylfluorodiazirine



pentafluorophenylbromodiazirine **4c** and conversion of the latter to the desired fluorodiazirine **4b** by a diazirine exchange reaction with tetrabutylammonium fluoride.[10,11] Fluorodiazirine **4b** was characterized by IR, UV, and ^{13}C and ^{19}F NMR spectroscopy.[11] In particular, the UV spectrum in pentane revealed maxima at 323 and 338 nm. Note that diazirine **4c** was used only as a relay compound in the preparation of fluorodiazirine **4b**. No doubt photolysis of **4c** would provide pentafluorophenylbromocarbene and a parallel series of products (**7-Br**–**10-Br**).

Laser flash photolysis (LFP) of diazirine **4a** in pentane generated PFPCCl (**2**) which displayed π(phenyl) → p(carbene) absorptions at 300 and 372 nm and a σ(carbene) → p(carbene) absorption at 596 nm.[8] LFP of diazirine **4b** produced PFPCF (**3**) which afforded a similar UV–vis spectrum; cf. Figure 1. Here, charge-transfer type transitions from the nearly degenerate set of high-lying phenyl π orbitals to the vacant carbenic p orbital are responsible for the absorptions at 292 and 324 nm, whereas the weak absorption at 564 nm is associated with electron promotion from the carbene's filled σ orbital (HOMO) to its vacant p orbital (LUMO). The absorptions are computed[11,12] at 271 nm (f = 0.287), 342 nm (f = 0.051), and 621 nm (f = 0.0045).

Both PFPCCl and PFPCF give intense *N*-ylide spectra with pyridine in pentane. The ylides, **6a** and **6b**, each absorbed at 468 nm and formed very rapidly with $k = 8.1 \times 10^9\ M^{-1}\ s^{-1}$ (**6a**) or $6.4 \times 10^9\ M^{-1}\ s^{-1}$ (**6b**).[11]



6a, X = Cl
6b, X = F

Although PFPCH (**1**) possesses a triplet ground state,[7] computational studies at the CCSD(T) level give a singlet ground state for PFPCCl (**2**), with $\Delta G_{S\text{-}T}$ = 4.2 kcal/mol.[8,13] Similar calculations show that $\Delta G_{S\text{-}T}$ = 14.9 kcal/mol in PFPCF (**3**).[11] Singlet states of carbenes are more sensitive to substituents than triplet states, and the singlet state of PFPCF is preferentially stabilized by the strong π-donating/σ-withdrawing abilities of the fluoro substituent.

PFPCCl and PFPCF readily cyclopropanated a series of olefins, including tetramethylethylene, 2-ethyl-1-butene, *trans*-butene, and *cis*-butene; cf. Scheme 2. Additionally, both carbenes inserted into the tertiary C–H bond of adamantane.

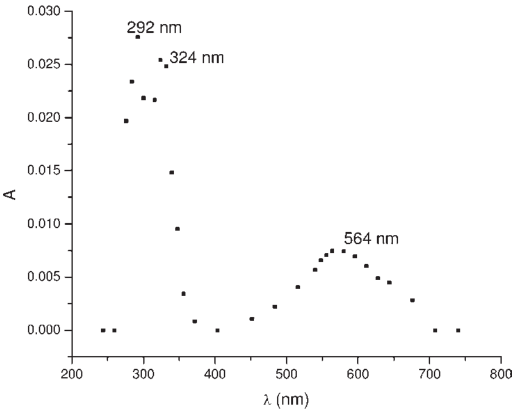


Figure 1. Calibrated UV–vis spectrum of PFPCF (**3**) in pentane 200 ns after laser pulse; π (phenyl) → p(carbene) absorptions at 292 and 324 nm, σ(carbene) → p(carbene) absorption at 564 nm.

Olefin-pentane solutions containing diazirine **4a** or **4b** were irradiated for 18 h in Pyrex tubes with a 200 W focused Osram XE mercury lamp at room temperature. The cyclopropane products were isolated from the solvent-stripped residues by column chromatography over silica gel with pentane elution. The products are shown in structures **7**–**10**; their identities were established by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and by mass spectroscopy.[11] Isolated yields appear in Table 1 and range from 59 to 87%. GC demonstrated product purities in excess of 95%.

In keeping with the singlet nature of PFPCCl and PFPCF, capillary GC analysis of their reaction products with *cis*- and *trans*-butene showed the products to have been formed with >99% stereospecificity. With PFPCF and *cis*-butene, where the *syn*-F and *anti*-F isomers of product **10-F** could be separated, NMR analysis indicated that the *syn*-F isomer predominated by a factor of 2.2.[14] This stereoselectivity resembles that observed with PhCF and *cis*-butene, where *syn*-F/*anti*-F was about 1.6.[15]

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[10] (a) Moss, R. A. *Acc. Chem. Res.* **2006**, *39*, 267. (b) Cox, D. P.; Moss, R. A.; Terpinski, J. *J. Am. Chem. Soc.* **1983**, *105*, 6513.

[11] See the Supporting Information for details.

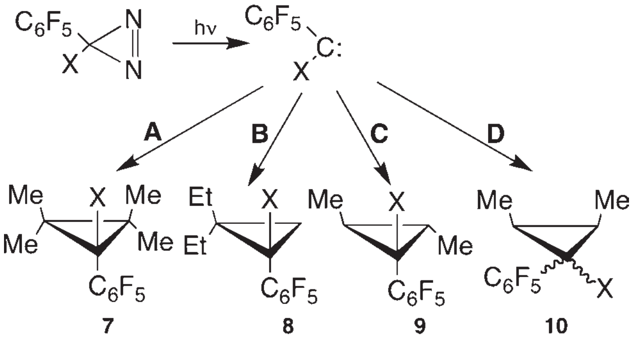
[12] Results obtained at the TD-B3LYP/6-311+G(d)//B97D/6-311+G(d) level applying the polarizable conductor self-consistent reaction field model (CPCM) and *n*-pentane as the solvent.

[13] CCSD(T) denotes a calculation based on the Coupled Cluster method that includes single and double excitations fully and triple excitations via perturbation theory. With this methodology, $\Delta G_{S\text{-}T}$ = −5.6 kcal/mol for PFPCH, with the triplet state being more stable than the singlet state.[8]

[14] In the ^{19}F NMR spectrum, the *syn*-F isomer has the more shielded F atom and the smaller *vic*-H–F coupling.[11,15]

[15] (a) Moss, R. A.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3828. (b) Moss, R. A.; Przybyla, J. *Tetrahedron* **1969**, *25*, 647.

Scheme 2. Preparation of Cyclopropanes



X = Cl or F

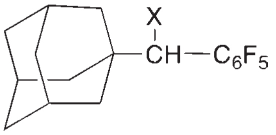
Alkenes: **A** = tetramethylethylene;
B = 2-ethyl-1-butene; **C** = *trans*-butene;
D = *cis*-butene

Table 1. Isolated Yields of Cyclopropane Products

cyclopropane	X = Cl (%)	X = F (%)
7	83	59
8	73	80
9	78	81
10	87[a]	77[b]

[a] The syn and anti isomers of **10-Cl** could not be separated. [b] 53% yield of *syn*-F isomer; 24% yield of *anti*-F isomer.

Photolysis of diazirines **4a** or **4b** with excess adamantane in benzene solution afforded C–H insertion products **11-Cl** or **11-F** in isolated yields of 30% and 45%, respectively. Structures were established by NMR and mass spectroscopy.[11]



11 (X = Cl,F)

We measured the absolute rate constants for additions of PFPCCl and PFPCF to tetramethylethylene (TME) and 2-ethyl-1-butene and compared these data to the analogous rate constants for additions of PhCCl and PhCF.[16] In these LFP experiments, we monitored the pseudo-first-order rate constant for carbene decay as a function of alkene concentration in pentane.[11] The derived second-order addition rate constants are collected in Table 2.

Table 2. Absolute Rate Constants for Carbene-Alkene Additions[a]

alkene	PFPCCl[b]	PhCCl	PFPCF[b]	PhCF
TME[c]	1.3×10^9	2.8×10^8 [d]	1.8×10^9	1.6×10^8 [d]
2-E-1-B[e]	1.1×10^8	6.3×10^6 [b]	1.7×10^8	7.8×10^5 [b]

[a] In pentane solution at 25 °C; rate constants in $\mathrm{M^{-1}\ s^{-1}}$. [b] This work. [c] Tetramethylethylene. [d] From ref 16. [e] 2-Ethyl-1-butene.

Both PFPCCl and PFPCF are highly reactive in addition reactions; with TME, $k_{\mathrm{add}} > 10^9\ \mathrm{M^{-1}\ s^{-1}}$, while, with the less nucleophilic 2-ethyl-1-butene, k_{add} is ~10 times smaller, but still exceeds $10^8\ \mathrm{M^{-1}\ s^{-1}}$.[17] Given that PhCCl is more reactive toward alkenes than PhCF,[16] it is somewhat surprising that PFPCF appears to be slightly more reactive than PFPCCl toward the two alkenes of Table 2.

The activating effect of the pentafluorophenyl group is evident from comparisons of k_{add} for PFPCCl with PhCCl and of PFPCF with PhCF (Table 2). The PFP carbenes are ~1–2 orders of magnitude more reactive than their nonfluorinated phenyl analogues. The PFP group is more electron-withdrawing than the phenyl group,[8] which destabilizes PFPCX relative to PhCX and enhances the reactivity of PFPCX.

In conclusion, PFPCCl and PFPCF are highly reactive singlet carbenes and effective carriers of fluorine labels via addition to alkenes or insertion into C–H bonds.

Acknowledgment. We are grateful to the National Science Foundation for financial support.

Supporting Information Available. Spectra of diazirines, ylides, and products **7**–**10** (X = Cl, F); details of kinetics and computations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Moss, R. A.; Lawrynowicz, W.; Turro, N. J.; Gould, I. R.; Cha, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7028.

(17) A competition experiment between the insertion of PFPCF into adamantane and its addition to 2-ethyl-1-butene led to an estimated $k_{\mathrm{ins}} = 2.1 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$, statistically corrected for the presence of 4 equivalent tertiary C–H bonds in adamantane.