Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 5551–5554

Tetrahedron Letters

Presumptive evidence for an intermediate oxirane in the reaction of phenylfluorocarbene with cyclohexenone

Robert A. Moss,* Lei Wang and Ronald R. Sauers*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, NJ 08903, United States

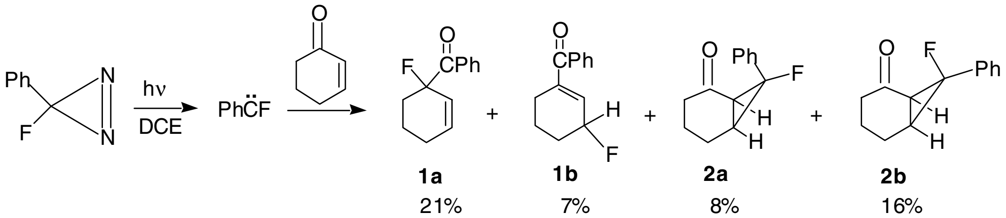
Received 3 May 2007; accepted 21 May 2007
Available online 24 May 2007

Abstract—Reaction of phenylfluorocarbene with 2-cyclohexen-1-one affords cyclopropane isomers **2a** and **2b** via C=C addition, as well as the fluoroketone isomers **1a** and **1b**, apparent rearrangement products of oxiranes **3** formed by carbene addition at C=O.

In the course of our studies of the reactions of carbanions derived from carbenes,[1] we had occasion to examine the reactions of phenylfluorocarbene (PhCF) and the corresponding phenylhalomethide carbanions ($PhCXF^-$) with 2-cyclohexen-1-one. Here, we describe evidence for the unexpected involvement of an oxirane (C=O addition), as well as cyclopropane formation (C=C addition), in these reactions of the moderately electrophilic and selective PhCF.[2] To our knowledge, this is the first report of competitive carbenic C=O and C=C additions to an enone substrate.[3]

Photolysis of phenylfluorodiazirine[4] with a twofold molar excess of cyclohexenone in 1,2-dichloroethane (DCE) gave 4 adducts of PhCF and cyclohexenone (all with M^+ at *m*/*e* 204), as well as (2+2) photodimers of cyclohexenone, and small quantities of the azine derived from attack of the carbene on the diazirine (PhFC=N–N=CFPh). The products were separable by GC,[5] and the adducts were isolated and purified by column chromatography on silica gel with pentane/ether elution. The key products are shown in Scheme 1, where the yields refer to isolated products, relative to the diazirine.

Assignments of the cyclopropane adducts, **2a** and **2b** are straightforward, based on their spectroscopic properties.[6] Thus, both are adducts of PhCF and cyclohexenone with molecular ions at *m*/*e* 204. Both display ketone carbonyl absorptions at 1693 cm^{-1}, with carbonyl carbon resonances apparent at (δ) 204–206 in their ^{13}C NMR spectra. Both isomers lack vinyl carbon or vinyl proton resonances in their respective NMR spectra, displaying instead appropriate cyclopropyl carbon and proton resonances. The isomers' configurations can be assigned from their ^{19}F NMR signals: *syn*-F isomer **2b** affords a more-shielded 'singlet' ^{19}F signal at δ −191.6, whereas *anti*-F isomer **2a** displays a less-shielded triplet at δ −132.6 ($J_{H–F} = 20$ Hz). It is known that *cis*-vicinal H–F coupling in a fluorocyclopropane



Scheme 1.

---

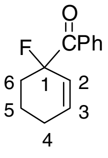
* Corresponding authors. Tel.: +1 732 445 2606; fax: +1 732 445 5312; e-mail: moss@rutchem.rutgers.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.124

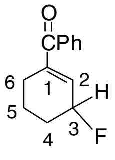
such as **2a** is $\sim$20 Hz, while trans-vicinal H–F coupling is significantly weaker.[7] Moreover, *syn*-F atoms (as in **2b**) are shielded by cis C–C bonds, relative to *anti*-F atoms (as in **2a**).[7]

Interestingly, the 2:1 stereoselectivity of the PhCF in favor of *syn*-F carbene addition to cyclohexenone (Scheme 1) is similar to the *syn*-F stereoselectivity of 1.5–1.7 for the addition of PhCF to *cis*-butene.[7a] Apparently, the α-carbonyl group of the cyclohexenone does not significantly perturb this facet of the addition.

Assignments of structures to products **1a** and **1b** are also based on spectroscopy.[6] Again, both are adducts of PhCF and cyclohexenone, with GC–MS molecular ions at *m*/*e* 204, and both contain benzoyl groups as indicated by fragments with *m*/*e* 105 (PhCO) and 77 (Ph). The IR spectra reveal strong ketone absorptions at 1686 cm^{-1} (**1a**) and 1654 cm^{-1} (**1b**, conjugated carbonyl). Corresponding ^{13}C NMR resonances are found at δ 199 (**1a**) and δ 198 (**1b**).



1a



1b

The ^{1}H NMR spectra support these assignments: **1a** presents two vinyl protons at δ 5.94 and 6.25, whereas **1b** has only a single vinyl proton at δ 6.43. The C-3 allylic proton of **1b** occurs at δ 5.20, deshielded by the *gem*-F atom, and split into a doublet of multiplets with $J_{\text{H–F}} = 47$ Hz; a complementary major splitting appears in the ^{19}F resonance (a doublet of multiplets) at δ −171.

Further evidence comes from the ^{13}C NMR spectra. For **1a**, the carbon atoms adjacent to F-substituted C-1 each show substantial 2-bond C–F coupling with splittings of 22 Hz (C-6 at δ 32.0), 28 Hz (C=O at δ 199), and 20 Hz (vinyl C-2 at δ 124.6). C-1, at δ 96.4, displays $^1J_{\text{C–F}} = 178$ Hz, while vinyl C-3 at δ 130.2 shows only a small (6.5 Hz) 3-bond C–F splitting. For **1b**, the carbonyl carbon at δ 198 reveals only a minor (4.6 Hz) long-range C–F splitting. Vinyl C-1 at δ 142.8 displays $^3J_{\text{C–F}} = 9$ Hz, while vinyl C-2 at δ 136 reveals $^2J_{\text{C–F}} = 19$ Hz. Alkyl C-4 at δ 28.9 gives $^2J_{\text{C–F}} = 19$ Hz and allylic, F-deshielded C-3 at δ 86.2 displays the expected large $^1J_{\text{C–F}} = 165$ Hz.

The most reasonable origin for products **1a** and **1b** is the rearrangement of the unstable and unisolated primary product oxirane isomers **3**, formed by PhCF addition across the carbonyl group of cyclohexenone; cf., Scheme 2. Ring opening of **3** affords ion pair **4**, which collapses to **1a** and **1b**. The ion pair must be tight and short-lived because the destabilizing effect of the benzoyl substituent at C-1 does not prevent least-motion product **1a** from dominating.

As shown in Table 1, the product distribution reported in Scheme 1 is somewhat dependent on the reaction conditions. Granting a certain variability due to product instabilities, it is clear that the oxirane-derived products **1a** and **1b** are favored by the more polar solvent DCE, and disfavored by the less polar solvent pentane, where the conventional cyclopropane adducts **2a** and **2b** are dominant. Moreover, in the presence of added TBAF or TBABr, where the phenylhalomethide carbanions PhCF$_2^-$ or PhCFBr$^-$ are present, as well as PhCF,[1] cyclopropanation is preferred over oxirination, even in DCE. We attribute this to predominant Michael addition of the carbanions to cyclohexenone at C-3, followed by cyclization (with halide loss)[1] to cyclopropanes **2a** and **2b**. The Michael addition carbanion pathway is superimposed on the addition of PhCF (at C=C and C=O), which otherwise favors C=O addition in DCE.

One can imagine that cyclohexenone might initially react with PhCF to generate carbonyl ylide **5**, which could then close to oxiranes **3**. Ylide **5** should be stabilized by increasing solvent polarity, and could thus account for the increase of oxirane-derived products in DCE relative to pentane. Indeed, laser flash photolysis (LFP)[8] of phenylfluorodiazirine in DCE containing 0.01 M cyclohexenone reveals the π→p and σ→p absorptions of PhCF at 304 and 544 nm, respectively,

Table 1. Product distributions for Scheme 1[a]

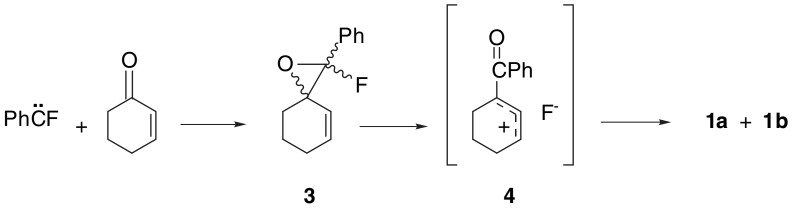
Solvent	Salt	**1a**/**1b**	**2a**/**2b**	(**1a** + **1b**)/(**2a** + **2b**)
Pentane		3.3	0.47	0.22
DCE		3.1	0.52	1.2
DCE[b]		5.4	0.46	1.2
DCE	TBAF[c]	2.0	0.60	0.58
DCE	TBABr[d]	2.0	0.36	0.53

[a] 2 equiv of cyclohexenone (relative to the diazirine) at 25 °C. Analysis by GC.[5]

[b] 10 equiv of cyclohexenone.

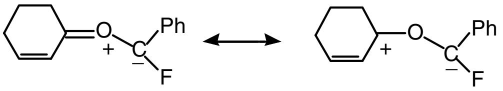
[c] 2 equiv of tetrabutylammonium fluoride.

[d] 2 equiv of tetrabutylammonium bromide.



Scheme 2.

as well as an absorption at 432 nm which grows in ($k = 4.0 \times 10^5\ s^{-1}$) to replace the carbene absorptions. We attribute this absorption to ylide **5**. In support of this assignment, we find that RB3LYP/6-311 + G(d)/RB3LYP/6-31G(d) calculations[9] predict a strong absorption for **5** at 455 nm ($f = 0.98$).



5

Nevertheless, it is not certain that ylide **5** is the precursor of oxiranes **3** and thus of ketones **1a** and **1b**. Although B3LYP/6-31G(d) calculations[9] indicate that the formation of **5** from PhCF and cyclohexenone is exothermic by 20 kcal/mol, we are unable to locate a pathway for closure of the ylide to the oxirane. Computationally, we find activation energies (in vacuo) of 2.4 and 6.1 kcal/mol for *direct* additions of PhCF to the C=C and C=O sites of cyclohexenone, respectively. Intrinsic reaction coordinate calculations connect the respective transition states to products **2** and **1** with exothermicities of 60 and 58 kcal/mol.[10]

LFP studies[8] indicate that PhCF (monitored at 304 nm) is quenched by cyclohexenone with $k_q = 8.3 \times 10^6\ M^{-1}\ s^{-1}$, whereas $PhCF_2^-$ (monitored at 448 nm) is quenched slightly more rapidly, with $k_q = 1.6 \times 10^7\ M^{-1}\ s^{-1}$. The second order rate constant for the quenching of PhCF by cyclohexenone is roughly competitive (and consistent) with the estimated second order rate constant for the formation of ylide **5** from the ketone and PhCF; viz. $k_f \approx 4 \times 10^7\ M^{-1}\ s^{-1}$, where $k_f = k_\psi$/[cyclohexenone], with $k_\psi = 4 \times 10^5\ s^{-1}$ and [cyclohexenone] = 0.01 M (see above).

Carbenic additions to carbonyl groups to form oxiranes (whatever the mechanism[11]) are uncommon, but not unknown. Lithium carbenoids such as Me_2CLiBr,[12a] RCHLiBr,[12b] $LiCHBr_2$,[12b] and Cl_2CHLi[12c,d] add as carbanions to aldehydes and ketones, ultimately giving oxiranes. Similarly, nucleophilic carbenes and silyenes form oxiranes, with the reaction presumably initiated by attack of the $\delta(-)$-carbenic carbon at the substrate's carbonyl carbon. Examples include dimethoxycarbene,[13a] siloxycarbenes,[13b] phosphanylsilycarbenes,[13c] and bis-trimethylsilylcarbene.[13d] Dihalocarbenes can add to highly halogenated ketones, for example, *sym*-tetrafluorodichloroacetone.[14] Finally, several quite reactive carbenes add to benzaldehyde, acetone, or benzophenone in reactions initiated by carbonyl ylide formation. Examples include methylene,[15a] bis-carbonylmethoxycarbene,[15b] diphenylcarbene,[15c] and fluorenylidene.[15d] However, oxirane formation between an enone and a moderately electrophilic species like PhCF appears to be unprecedented.

Preliminary experiments indicate that the reactions of phenylchlorocarbene with both cyclohexenone and cyclopentenone proceed analogously to the reaction of PhCF with cyclohexenone. Details of these reactions, and of reactions with other enones, will be described in a full paper.

Acknowledgments

We are grateful to the National Science Foundation for financial support. R.R.S. thanks the National Center for Computer Applications for time on the IBM P Series 690. We thank Dr. Seho Kim for assistance with several NMR spectra, and Professor Spencer Knapp for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the on-line version, at doi:10.1016/j.tetlet.2007.05.124.

References and notes

1. (a) Moss, R. A.; Tian, J. *J. Am. Chem. Soc.* **2005**, *127*, 8960; (b) Moss, R. A.; Tian, J. *Organic Lett.* **2006**, *8*, 1245; (c) Moss, R. A.; Tian, J. *Tetrahedron Lett.* **2006**, *47*, 3419.
2. The selectivity and electrophilicity of PhCF ($m_{obsd} = 0.89$) are rather similar to those of CCl_2 ($m = 1.00$ by definition); see: Moss, R. A. Carbenic Philicity. In *Carbene Chemistry from Fleeting Intermediates to Powerful Reagents*; Bertrand, G., Ed.; Dekker-Fontis: New York, 2002; p 57f; See also: Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15; Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.
3. See below for a brief discussion of the literature.
4. Moss, R. A.; Terpinski, J.; Cox, D. P.; Denney, D. Z.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1985**, *107*, 2743.
5. We used a 30 m × 0.53 mm 5% cross-linked phenylmethylsiloxane capillary column with a 1.5 μm film of the siloxane. The oven temperature was initially 50 °C (3 min), and was programed at 30 °C/min to a final temperature of 260 °C. The He carrier gas flow rate was 3.9 mL/min. Retention times (min): **1a**, 10.0; **1b**, 10.3; **2a**, 10.2; **2b**, 10.6.
6. See Supplementary data for full descriptions of the spectroscopic information.
7. (a) Moss, R. A.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3828; (b) Moss, R. A.; Przybyla, J. R. *Tetrahedron* **1969**, *25*, 647.
8. For a description of our LFP system, see Supplementary data.
9. Frisch, M. J. et al. See Supplementary data for the complete reference to GAUSSIAN 03, and for computational details.
10. The calculations predict preferential formation of cyclopropanes **2** in vacuum, which accords with our results in pentane solvent. However, a similar dominance is predicted in (simulated) DCE, where the oxirane-derived products (**1**) are found to dominate.
11. PhCF does not add to cyclohexanone to form an oxirane, although LFP detects a possible ylide at 448 nm.
12. (a) Cainelli, G.; Tangari, N.; Ronchi, U. *Tetrahedron* **1972**, *28*, 3009; (b) Villieras, J.; Bacquet, C.; Normant, J.-F. *Bull. Soc. Chim. France* **1975**, 1797; (c) Köbrich, G.; Grosser, J.; Werner, W. *Chem. Ber.* **1973**, *106*, 2610, 2620;

(d) Blumbergs, P.; LaMontagne, M. P.; Stevens, J. L. *J. Org. Chem.* **1972**, *37*, 1248.

13. (a) Dawid, M.; Venneri, P.; Warkentin, J. *Can. J. Chem.* **2001**, *79*, 110; (b) Brook, A. G.; Pearce, R.; Pierce, J. B. *Can. J. Chem.* **1971**, *49*, 1622; (c) Illa, O.; Gornitzka, H.; Branchadell, V.; Baceiredo, A.; Bertrand, G.; Ortuño, R. M. *Eur. J. Org. Chem.* **2003**, 3147; (d) Barton, T. J.; Hoekman, S. K. *J. Am. Chem. Soc.* **1980**, *102*, 1584.
14. Seyferth, D.; Tronich, W.; Smith, W. E.; Hopper, S. P. *J. Organomet. Chem.* **1974**, *67*, 341.
15. (a) Bradley, J. N.; Ledwith, A. *J. Chem. Soc.* **1963**, 3480; (b) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4953; (c) Tomioka, H.; Miwa, T.; Suzuki, S.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 753; (d) Scaiano, J. C.; McGimpsey, W. G.; Casal, H. L. *J. Am. Chem. Soc.* **1985**, *107*, 7204.