[3 + 2] Methylenecyclopentane Annulations of Unactivated and Electron-Rich Olefins with 2-(Phenylsulfonyl)-1-methylenecyclopropanes

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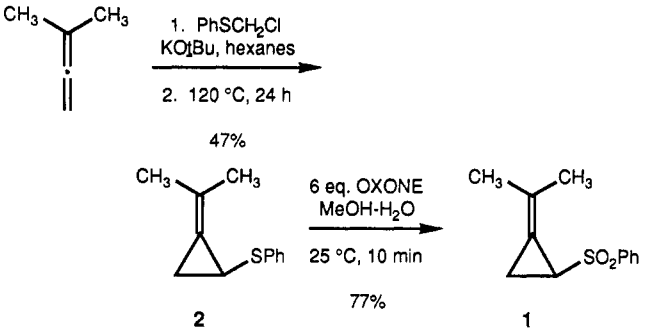
Received February 20, 1990

Summary: The thiyl radical catalyzed reaction of **1** with unactivated and electron-rich olefins affords methylenecyclopentanes regiospecifically. Using irradiation in the presence of dibutyl disulfide, these reactions can be achieved using equimolar amounts of olefins.

A multitude of [3 + 2] cycloaddition-type methods for cyclopentane ring synthesis have been developed in recent years,[1,2] but extensive limitations remain. Most have as a major restriction the required use of olefins activated with electron-withdrawing groups, and many suffer from harsh reaction conditions or a lack of regioselectivity. Some are only efficient in specialized cases or intramolecularly. Radical-mediated annulations avoid these problems in cases, but most require large excesses of the olefin being annulated,[2b-d,3] which severely restricts the range of their utility. We are pleased to report a new annulation, the thiyl radical catalyzed [3 + 2] annulation of olefins with methylenecyclopropanes, which appears to simultaneously overcome all of these limitations.

In seeking methods for the [3 + 2] annulation of unactivated olefins, the annulation reagent **1** was chosen for study because of its potential to form an electrophilic radical intermediate.[4] Slow addition of chloromethyl phenyl sulfide to a suspension of potassium *tert*-butoxide in 1,1-dimethylallene and hexanes followed by isomerization of the crude mixture of methylenecyclopropanes to the most stable isomer afforded **2**[5] [bp 70–72 °C (0.005 mm)] in 47% yield. Oxidation of **2** with sodium acetate buffered OXONE afforded **1** (mp 56.5–59 °C, from hexanes) in 77% yield.



2 **1**

Our first investigations centered on the thiyl radical catalyzed reaction of **1** with isobutyl vinyl ether (**3**). We were pleased to find that treatment of **1** and a 10-fold excess of **3** with 1 equiv of diphenyl disulfide and AIBN in refluxing benzene (procedure A) afforded the methylenecyclopentane **4**[6] regiospecifically in 69% yield.

This procedure was convenient for inexpensive olefins but required a large excess of the olefin due to the formation of 2-cyanopropyl radical derived byproducts, such as **5** in reactions with isobutyl vinyl ether. In seeking a better method for initiating these reactions, we attempted to use the direct formation of alkyl thiyl radicals by irradiation of dialkyl disulfides.[7] We were pleased to find that irradiation (>300 nm) of a mixture of **1** and a 5-fold excess of **3** in the presence of 10–25 mol % *n*-butyl disulfide and 10 mol % pyridine[8] (procedure B) afforded **4** in 81% yield. Most significantly, this procedure still works well when only 1.5 equiv of **3** was used (74%) or when a slight excess of **1** was used (62%, based on **3**). This procedure worked best with most olefins but was surprisingly ineffective with phenyl vinyl sulfide. Our results with other olefins are

(1) For some selected examples, see: (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. (b) Binger, P.; Germer, A. *Chem. Ber.* **1981**, *114*, 3325 and references therein. The special case of (diphenylmethylene)cyclopropane works with unhindered unactivated olefins: Binger, P.; Bentz, P. *Angew. Chem., Int. Ed. Engl.* **1982**, *18*, 622. (c) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. (d) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (e) Herndon, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 3165. Bucheister, A.; Klemarczyk, P.; Rosenblum, M. *Organometallics* **1982**, *1*, 1679. (f) Kurosawa, H.; Urabe, A.; Miki, K.; Kasai, N. *Organometallics* **1986**, *5*, 2002. (g) Beak, P.; Burg, D. A. *J. Org. Chem.* **1989**, *54*, 1647. (h) Marino, J. P.; Laborde, E. *J. Am. Chem. Soc.* **1985**, *107*, 734. (i) Tsuji, J.; Shimizu, I.; Ohashi, Y. *Tetrahedron Lett.* **1985**, *26*, 3825. (j) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391. (k) Berson, J. A.; Duncan, C. D.; Corwin, L. R. *J. Am. Chem. Soc.* **1974**, *96*, 6175. Stone, K. J.; Little, R. D. *J. Am. Chem. Soc.* **1985**, *107*, 2495 and references therein. (l) Tomioka, H.; Kobayashi, D.; Hashimoto, A.; Murata, S. *Tetrahedron Lett.* **1989**, *30*, 4685. (m) Miyashi, T.; Kamata, M.; Mukai, T. *J. Am. Chem. Soc.* **1986**, *108*, 2755.

(2) Radical mediated annulations of electron-poor olefins: (a) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. In a two-step reaction, Curran has applied his atom-transfer cycloaddition to an excess of unactivated olefin (1-hexene) using an iodopropargylmalonate: Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.*, in press. We thank Professor Curran for a preprint of his work: (b) Cekovic, Z.; Saicic, R. *Tetrahedron Lett.* **1986**, *27*, 5893. (c) Clive, D. J.; Angoh, A. G. *J. Chem. Soc., Chem. Commun.* **1985**, 980. (d) Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501.

(3) (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. Feldman, K. S.; Ruckle, R. E., Jr.; Romanelli, A. L. *Tetrahedron Lett.* **1989**, *30*, 5845. We thank Professor Feldman for a preprint of his work. For related reactions, see: Feldman, K. S.; Fisher, T. E. *Tetrahedron* **1989**, *45*, 2969. Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985. (b) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. These reactions utilize 50 equiv of the reacting olefin.

(4) For recent reviews of free-radical reactions in organic synthesis, see: (a) Curran, D. P. *Synthesis* **1988**, 417. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(5) Satisfactory elemental analyses and/or exact mass molecular weights have been obtained on all new compounds. In all cases, ^1H and ^{13}C NMR and IR spectral data were consistent with the assigned structures.

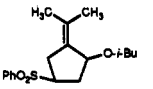
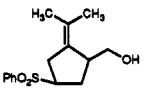
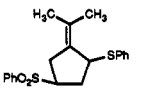
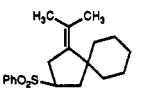
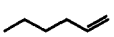
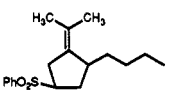
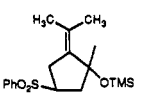
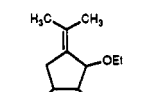
(6) The stereochemistry of the major isomers of **4** and **14** were assigned from dNOE studies, where the appropriate 1,3-enhancement was observed in each case. No NOE was observed in the minor isomer. The stereochemistry of the major isomer of **16** was assigned by potassium *tert*-butoxide catalyzed equilibration, in which the kinetically minor product was found to be thermodynamically predominant (>4:1). The trans isomer is predicted by molecular mechanics calculations (MM2, Macromodel) to be ca. 1 kcal more stable. The validity of the calculations is supported by the observation of the same result in **14**. The trans isomer is more stable because it can best avoid allylic strain from the isopropylidene group. See: Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773. Johnson, F. *Chem. Rev.* **1968**, *68*, 375. The stereochemistry of the major isomer of **13** was tentatively assigned from a strong similarity of chemical shifts and coupling patterns with the major isomers of **14** and **16**. Comparisons of actual and modeled coupling constants for **4** and **14** also tentatively indicated the assigned structures.

(7) Dialkyl disulfides show a tailing absorption which extends pass 300 nm ($\epsilon \approx 10$): Calvert, J. G.; Pitts, J. N. *Photochemistry*; Wiley: New York, 1961; p 490.

(8) Pyridine inhibits the occasional formation of acid-catalyzed products.

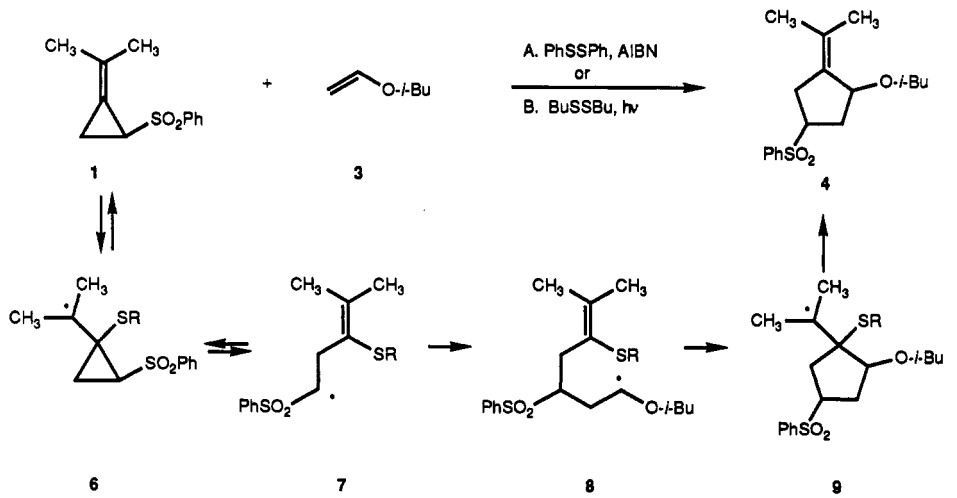
0022-3263/90/1955-4780$02.50/0

Table I. Annulation of Olefins with 1

olefin	equiv	procedure[a]	% yield	product	cis:trans[b]
	5	B	81		56:44
	1.5	B	74		54:46
	0.9	B	62		55:45
	10	A	69		58:42
				4	
	1.5	B	57		83:17
	0.9	B	53		82:18
	10	A	57		81:19
				13	
	10	A	88		80:20
				14	
	3	B	59		
	0.8	B	49		
	5	A	49		
				15	
	1.6	B	42		77:23
	20	A	47		76:24
				16	
	1.5	B	57		(39:61)[c]
	0.8	B	60		(40:60)[c]
	10	A	64		(33:67)[c]
				17	
	10	A	40		*d*
				18	

[a] Procedure A: 80 °C, benzene, 0.5 equiv of AIBN, 1.0 equiv of PhSSPh, 16–48 h. Procedure B: *hν* (Rayonet photochemical reactor, 16 300-nm bulbs), 0.1–0.25 BuSSBu, neat. [b] See ref 6. [c] Stereochemistry not yet assigned. [d] Mixture of three isomers. A fourth isomer could not be obtained in pure form.

Scheme I



summarized in Table I. The methylenecyclopentanes are formed regiospecifically in good yields, and the ease with which allyl alcohol and methylenecyclohexane are annulated is particularly striking. No reaction occurs with dimethyl fumarate or phenyl vinyl sulfone.

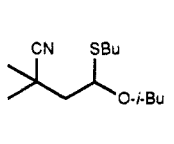
The mechanism of this reaction (Scheme I) is most easily envisioned as being analogous to that proposed by Feldman for the reaction of vinylcyclopropanes with olefins or oxygen.[3a,9] Irradiation of di-*n*-butyl disulfide generates *n*-butylthiyl radicals.[10] Addition of a thiyl radical to **1** to afford **6** apparently competes with recombination of thiyl radicals, causing the requirement of large amounts of initiator in procedure A. The cyclopropylcarbinyl radical **6** can then open to form the homoallylic radical **7**. The formation of **7** would seem to be reversible, as no reaction occurs in the absence of olefin. Addition of **7** to olefins to form the 5-hexenyl radical **8** may be surprisingly rapid, as the trapping of **7** with diphenyl disulfide has not been observed. The 5-hexenyl radical **8** may then close to give **9**, which may then regenerate the thiyl radical by elimi-

(9) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878.

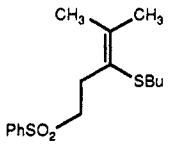
(10) Rao, P. M.; Knight, A. R. *Can. J. Chem.* **1968**, *46*, 2462.

nation to form 4. Notably, only the 5-*exo* ring closure can lead to regeneration of the thiyl radical.

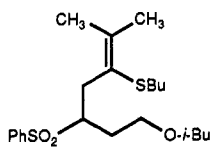
In support of this mechanism, the minor byproducts **10**, **11**, and **12** have been isolated from a reaction employing 1 equiv of dibutyl disulfide. The formation of these byproducts was minimized by using minimum amounts of dibutyl disulfide.



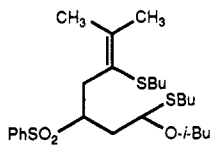
5



10



11



12

These mild reaction conditions should be tolerant of many functional groups. Because the reaction is effective with equimolar amounts of unactivated olefins, this and related reactions should be useful for the annulation of complex molecules. Radical chain reactions employing an addition–series of reactions–fragmentation sequence seem ideally suited for accomplishing intricate processes because the intermediate radicals are permitted long lifetimes while the chain transfer is very fast.[11] A wide range of methylenecyclopropanes may undergo similar reactions,[12] and there is potential for influencing the reaction's stereochemistry through the choice of catalyst. We are continuing to study the intriguing features of this reaction.

Acknowledgment is made to the Robert A. Welch Foundation and the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supplementary Material Available: Experimental procedures and spectral data for **1**, **2**, **4**, and **13–18** (4 pages). Ordering information is given on any current masthead page.

(11) For a discussion of ideality in free-radical chain reactions, see ref 4a, p 499.

(12) We have observed that the parent 2-(phenylsulfonyl)-1-methylenecyclopropane also annulates olefins in good yield. These studies will be reported in due course.

The Stereoselective Construction of (*Z*)-3-Aryl-2-fluoroalkenoates

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Received March 5, 1990

Summary: The use of 2,4,6-trimethylphenyl α-silyl-α-fluoroacetate in the Peterson olefination reaction leads to the highly stereoselective formation of (*Z*)-3-aryl-2-fluoroalkenoates via an aldol reaction most likely proceeding through an open transition state since stereocontrol of the enolate geometry was not possible.

Even though the stereoselective construction of 2-fluoroalkenoates may have broad general applicability in the preparation of biologically active materials[1] such as prostaglandins,[2] insect sex pheromones,[3] or steroids,[4] there are relatively few methods available for the synthesis of 2-fluoroalkenoate building blocks[5] or monofluoroalkenes generally.[6]

Table I. Products of Peterson Olefination Reaction of the Lithium Enolate of Ethyl α-(Trimethylsilyl)-α-fluoroacetate

$LiC(Si(CH_3)_3)FCO_2CH_2CH_3 + RR'CO \rightarrow RR'C{=}CFCO_2CH_2CH_3$

R	R′	*E*:*Z* stereoselectivity[a]
H	4-CH_3Ph	1:1.4
H	C_2H_5	1:4.0
H	Ph	1:2.7

[a] Determined by ^{19}F NMR spectroscopy.

Results and Discussion

We have found that α-fluoro-α-silylacetates **1** can be utilized in a highly stereoselective Peterson olefination procedure[7,8] to form (*Z*)-3-aryl-2-fluoroalkenoates and a

(1) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197.

(2) (a) Nakai, H.; Hamanaka, N.; Miyake, H.; Hayashi, M. *Chem. Lett.* **1979**, 1499–1502. (b) Grieco, P. A.; Schillinger, W. J.; Yokoyama, Y. *J. Med. Chem.* **1980**, *23*, 1077–1083. (c) Grieco, P. A.; Takigawa, T.; Vedananda, T. R. *J. Org. Chem.* **1985**, *50*, 3111–3115.

(3) Camps, F.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1986**, *42*, 3623–3629.

(4) Dauben, W. G.; Kohler, B.; Roesle, A. *J. Org. Chem.* **1985**, *50*, 2007–2010.

(5) (a) Matsuo, N.; Kende, A. S. *J. Org. Chem.* **1988**, *53*, 2304–2308. (b) Machleidt, H.; Wessendorf, R. *Justus Liebigs Ann. Chem.* **1964**, *674*, 1–10. (c) Tarrant, P.; Johncock, P.; Savory, J. *J. Org. Chem.* **1963**, *28*, 839–843. (d) Bergmann, E. D.; Shahak, I.; Sali, E.; Aizenshtat, Z. *J. Chem. Soc. C* **1968**, 1232–1235. (e) Dedek, V.; Kovak, M. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2660–2671. (f) Kobayashi, Y.; Morikawa, T.; Yoshizawa, A.; Taguchi, T. *Tetrahedron Lett.* **1981**, *22*, 5297–5300. (f) Nakayama, Y.; Kitazume, T.; Ishikawa, N. *J. Fluorine Chem.* **1985**, *29*, 445–448. (g) Pawson, B. A.; Chan, Ka-K.; DeNoble, J.; Han, Ru-J. L.; Piermattie, V.; Specian, A. C.; Srisethnil, S. *J. Med. Chem.* **1979**, *22*, 1059–1067. (h) Normant, J. F.; Reboul, O.; Sauvetre, R.; Deshayes, H.; Masure, D.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 2072–2078. (i) Elkik, E.; Francesch, C. *C. R. Acad. Sci. Paris C* **1970**, *270*, 443–445. (j) Elkik, E.; Francesch, C. *C. R. Acad. Sci. Paris C* **1971**, *271*, 1022–1024. (k) Elkik, E. *Bull. Chim. Soc. Fr.* **1968**, 1371–1374. (l) Elkik, E. *Bull. Chim. Soc. Fr.* **1964**, 2258–2262. (m) Elkik, E. *Bull. Chim. Soc. Fr.* **1967**, 1569–1571.

(6) (a) Bessiere, Y.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1739–1746. (b) Taguchi, T.; Takigawa, T.; Tawara, Y.; Morikawa, T.; Kobayashi, Y. *Tetrahedron Lett.* **1984**, *25*, 5689–5692. (c) Cox, D. G.; Garusamy, N.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 2811–2812. (d) Daub, G. W.; Zuckermann, R. N.; Johnson, W. S. *J. Org. Chem.* **1985**, *50*, 1599–1602. (e) Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 2445–2447. (f) McCarthy, J. R.; Peet, N. P.; LeTourneau, M. E.; Inbasekaran, M. *J. Am. Chem. Soc.* **1985**, *107*, 735–737.

(7) (a) Ager, D. J. *Synthesis* **1984**, 384–398. (b) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281–283. (c) Boeckman, R. K., Jr.; Chinn, R. L. *Tetrahedron Lett.* **1985**, *26*, 5005–5008. (d) Larson, G. L.; Quiroz, F.; Suarex, J. *Synth. Commun.* **1983**, *13*, 833–844. (e) Hartzell, S. L; Rathke, M. W. *Tetrahedron Lett.* **1976**, 2757–2760. (f) Hudrlik, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263–2264. (g) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620–1621.

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