Table I

Olefin	Peracid	Relative Rates: $Mo(CO)_6$ *t*-BuOOH	Relative Rates: $VO(acac)_2$ *t*-BuOOH
	Part A[c]		
Cyclohexene (**9**)	1[a]	1	1
2-Cyclohexen-1-ol (**10**)	0.55[a] (92/8)[7]	4.5 (98/2)	>200 (98/2)
1-Acetoxy-2-cyclohexene (**11**)	0.046[a] (37/63)[7]	0.07 (40/60)	
3-Cyclohexen-1-ol (**7**)	0.42[a] (60/40)[7]	11.0 (98/2)	10.0 (98/2)
	Part B		
trans-5-Decene (**12**)		1	1
1-Hydroxy-(*E*)-4-nonene (**13**)		0.98	13.4
	Part C[d]		
Geraniol (**1**)	0.5	45	~100
Geranyl acetate (**14**)	0.04		
Linalool (**3**)	0.11	0.62	10.3

[a] With the exception of the peracid relative rates (ref 4b) in part A all the data in this table are from the present work. [b] All the competition studies were carried to about 5% completion based on "total olefin" (*i.e.*, based on number of moles of double bonds present, thus 1 mol of geraniol = 2 mol of cyclohexene) by limiting the amount of *t*-BuOOH added. The ratios of the epoxide products were determined by glc. All reactions were run at reflux in benzene with a "total olefin" concentration of 0.35 *M*. [c] In part A the figures in parentheses refer to (% *syn*-epoxide/*anti*-epoxide). It is important to note that the relative rates in part A apply only in vertical columns (*i.e.*, no correlation of rates has been made for the different reagents). [d] Unlike parts A and B, in part C the double bonds in competition are in the same molecule and each entry corresponds to the ratio of epoxidation at the double bond proximate to the oxygen function *vs.* the double bond further removed from it.

results with peracids, one notes that the vanadium and molybdenum catalyzed epoxidations of the allylic alcohol **10** and even the homoallylic alcohol **7** are essentially stereospecific. Furthermore, alcohols **10** and **7** were oxidized considerably faster than cyclohexene in both of the transition metal systems. It is interesting that the molybdenum system reacted faster with the homoallylic alcohol **7** than with the allylic alcohol **10**, whereas with the vanadium catalyst the opposite was true.

Even the bishomoallylic alcohol **13**[8] is epoxidized by the vanadium system over ten times faster than the purely hydrocarbon olefin **12** (Table I, part B). These olefins (**12** and **13**) exhibit identical reactivity toward the molybdenum system. The above result suggests that the vanadium catalyst may be capable of selective epoxidation of the 6,7 double bond in natural polyene alcohols such as squalene-2,3-glycol.

Both geraniol (**1**) and geranyl acetate (**14**) are epoxidized by peracids preferentially at the olefinic site ($\Delta^{6,7}$) furthest removed from the hydroxyl group (Table I, part C). Indirect epoxidation *via* bromohydrin formation would also favor the more electron-rich 6,7 double bond. As expected from the results in part A, the molybdenum- and vanadium-hydroperoxide systems showed high regioselectivity for the 2,3 double bond or geraniol. Even the vinyl group of linalool was selectively epoxidized by the vanadium reagent which is exceptionally reactive toward allylic alcohols. Although we have not measured any absolute rates, we have made the qualitative observation that the molybdenum catalyst is faster with most olefins than the vanadium catalyst. The exceptions occur with allylic alcohols, where the rate accelerations are so great with the vanadium catalyst that the absolute rates actually exceed those with the molybdenum catalyst.

We are continuing our studies on the mechanism[9] and synthetic utility of these transition metal catalyzed epoxidations. The rate accelerations and high stereoselectivities observed in the present work clearly support mechanisms[2b] where the alcohol is coordinated to the metal in the rate determining step. It would not be surprising if olefinic acids and amides showed similar synthetically useful effects with these reagents.

Acknowledgment. We are grateful to Professor Robert Ireland of the California Institute of Technology for kindly providing a sample of 4β-hydroxycholesterol. We thank the National Science Foundation (GP-30485X), Hoffmann-La Roche Inc., and the Mobil Foundation for support of this research.

(8) Alcohol **13** was produced by reaction of butyllithium with dihydropyran as described by F. L. M. Pattison and R. E. A. Dear, *Can. J. Chem.*, **41**, 2602 (1963).

(9) K. B. Sharpless, J. M. Townsend, and D. R. Williams, *J. Amer. Chem. Soc.*, **94**, 295 (1972).

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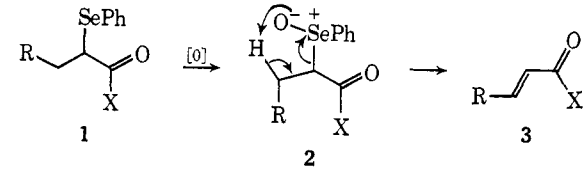
Electrophilic and Nucleophilic Organoselenium Reagents. New Routes to α,β-Unsaturated Carbonyl Compounds

Sir:

We recently established that alkylphenyl selenoxides undergo facile syn elimination to form olefins[1] and that this process can be useful for introducing unsaturation into organic structures under mild conditions.[1,2] We now report the application of organoselenium reagents to syntheses of α,β-unsaturated carbonyl compounds. In each case the penultimate step involves oxidation of an α-phenylselenocarbonyl compound (**1**) to the corresponding selenoxide **2** which eliminates at room temperature to the desired olefin **3**. We have found that X (**1**, Scheme I) can be hydrogen, alkyl, or alkoxy; thus

Scheme I



1 2 3

α,β-unsaturated aldehydes, ketones, and esters can be prepared by this method. The α-phenylselenocarbonyl compounds (**1**) are readily formed in a variety of ways from the previously employed[1,2] nucleophilic selenium reagent $PhSe^-Na^+$ (**4**) and from the electrophilic selenium reagents[3] PhSeCl (**5**) and PhSeBr (**6**).

(1) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).
(2) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **95**, 2697 (1973).
(3) PhSeCl (**5**) and PhSeBr (**6**) are obtained in quantitative yield when PhSeSePh (ref 2) is cleaved with sulfuryl chloride or bromine, respectively. Although both of the benzene selenyl halides are stable solids, it is often more convenient to prepare them *in situ* from the diselenide.

In the case of ketones and aldehydes the α-phenylseleno moiety is introduced by simply reacting an ethyl acetate solution of the carbonyl compound with PhSeCl (**5**) at room temperature.[4] Oxidation with hydrogen peroxide or sodium periodate, in the same reaction vessel, produces the unsaturated compound (Table I).

Table I. Conversion of Aldehydes and Ketones to Their α,β-Unsaturated Analogs[a]

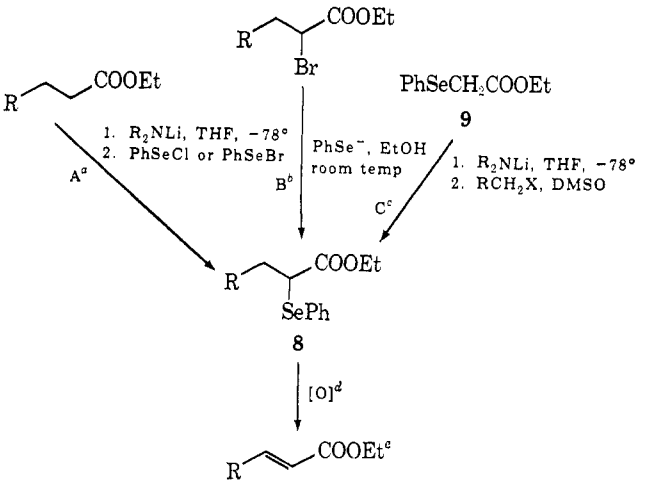
Compd (time for PhSeCl addition, hr)	% yield[b] of unsaturated product (% recovered starting material)	Oxidant (time for elimination, hr)
4-*tert*-Butylcyclohexanone (0.25)	74 (5)	H_2O_2 (0.75)
	45 (5)	CH_3CO_3H (0.75)
4-Acetoxycyclohexanone (1)	53 (12)	H_2O_2 (0.75)
	47 (10)	$NaIO_4$[c] (0.75)
Cyclododecanone (5)	77 (5)	H_2O_2 (1)
	75 (5)	CH_3CO_3H (1)
3-Cholestanone (0.75)	84[d] (4)	H_2O_2 (0.75)
4-Heptanone (5)	64 (13)	H_2O_2 (1)
2-Heptanone[e] (2)	34 (29)	H_2O_2 (0.5)
Propiophenone[e] (35)	84 (7)	$NaIO_4$[c] (1.5)
Hydrocinnamaldehyde[e] (36)	67 (8)	$NaIO_4$[c] (1)
Dodecylaldehyde[e] (20)	46 (13)	$NaIO_4$[c] (4)

[a] The reactions were carried out on a 1 mmol scale exactly as described for the larger scale preparation of $\Delta^{1,2}$-cholestenone. [b] These are absolute yields determined by glc relative to internal standards. In these cases, where stereoisomeric enones could form, only the *E* isomers were detected. [c] When $NaIO_4$ was the oxidant, the crude α-phenylseleno ketone was dissolved in THF and 2 equiv of $NaIO_4$ in MeOH–H_2O (7:3) was added dropwise at room temperature: M. Cinquini, S. Colonna, and R. Giovini, *Chem. Ind. (London)*, 1737 (1969). [d] The major product was the $\Delta^{1,2}$-enone; the $\Delta^{4,5}$-enone and the dienone were formed in 3% and 4% yields, respectively, for a material balance of 95%. The starting material and the three products were readily separated on glc at 250° (4 ft × 1/8 in. glass column packed with 3% OV-17 on Gas Chrom Q); the retention times were ketone < $\Delta^{1,2}$-enone < $\Delta^{4,5}$-enone < dienone. The three unsaturated products were also isolated by preparative tlc (the R_f values follow the same order as the glc retention times) and identified by comparison with authentic samples. [e] In these cases, the addition of PhSeCl was accelerated by the addition of concentrated HCl.

A typical procedure is as follows. To a solution of 5.50 g (14.2 mmol) at 3-cholestanone in 125 ml of ethyl acetate was added 3.30 g (17.2 mmol) of PhSeCl[3] (**5**). The resulting red-orange solution was stirred until it had turned pale yellow (1 hr).[5] At this point 25 ml of water was added to the stirred reaction mixture.[6] After the aqueous phase had been drawn off, 55 ml of THF was added and 3.5 ml (40.6 mmol) of 30% H_2O_2 was added dropwise, keeping the temperature below 35°; stirring was continued for 1 hr. The reaction mixture was washed with water and Na_2CO_3 solution, dried, and concentrated to give 5.25 g (96%) of crude product. Recrystallization from EtOH gave 2.43 g (45%) of the pure $\Delta^{1,2}$-cholestenone, mp 95–97°. The oily residue consisted mainly of the $\Delta^{1,2}$ isomer.

As shown in Scheme II the α-phenylseleno esters (**8**) were prepared in three different ways and were oxidized without isolation to the unsaturated esters in fair to good over-all yields (Table II). Paths A and C are slight modifications of Rathke's procedures for the generation of ester enolates and their reactions with iodine[7] and alkyl halides,[8] respectively.[9] The selenium reagent **9** [bp 100–102° (1 mm)] required for path C was easily prepared by reaction of α-chloroethyl acetate with $PhSe^-Na^+$ (**4**) in ethanol.[2]

Scheme II



[a] PhSeBr and PhSeCl work equally well and the bromide is more conveniently prepared *in situ*. For the general procedure see preparation of (*E*)-methyl dodec-2-enoate below. [b] Procedure B is identical with that described in ref 2 except that the α-bromo ester substituted for the epoxide. [c] The alkylation of (used EtBr and $PhCH_2Br$) phenylseleno ester **9** (procedure C) was performed exactly as described by Rathke[8] for the alkylation of simple esters. Ethyl acetate was used for extraction of the crude seleno esters **8**, and after aqueous wash, ~2 equiv of 40% peracetic acid was added to the organic phase resulting in rapid formation of the unsaturated esters (Table II, path C). [d] Although in the ketone case peracids often gave poorer yields than H_2O_2, both reagents were equally effective for the oxidation of α-phenylseleno esters. [e] The *E* esters were the only products detected in these eliminations.

Table II. Unsaturated Esters Produced According to Scheme II

	Yield[a] of R–CH=CH–CO_2Et		
	Path A	Path B	Path C
R = Ph	80	78	65
R = CH_3	83	89	60
R = *n*-C_9H_{19}	79	82	

[a] These are absolute yields determined by glc relative to internal standard.

(4) There are several precedents for the addition of ArSeX (X = Cl and SCN) to ketones; see D. L. Klayman in "Organic Selenium Compounds," D. L. Klayman and W. H. H. Günther, Ed., Wiley-Interscience, New York, N. Y., 1973, Chapter 4. However, the parent compound PhSeCl had never been added to ketones and no selenium electrophile had ever been added to aldehydes. It should be pointed out that brominations of aldehydes are generally unsuccessful due to oxidation to the acyl bromide. PhSeBr cannot be substituted for PhSeCl in these additions (for the problems encountered upon attempted addition of *o*-nitrophenylselenenyl bromide to acetone see H. Rheinboldt and M. Perrier, *Bull. Soc. Chim. Fr.*, **17**, 759 (1950)). Recently, we have found that the α-selenation of ketones with PhSeCl can be carried out in the presence of other functional groups such as alcohols, esters, and even certain double bonds (R. F. Lauer and K. B. Sharpless, unpublished results).

(5) The time required for this addition seems to depend as with brominations on the rate of acid catalyzed enolization of the carbonyl compound.

(6) It is essential to remove the HCl prior to oxidation.

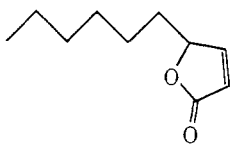
(7) M. W. Rathke and A. Lindert, *Tetrahedron Lett.*, 3995 (1971).

(8) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).

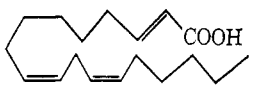
(9) It should be pointed out that the anion derived from seleno ester **9** (path c) is not the first selenium stabilized anion. Seebach and Peleties have reported a variety of such species: D. Seebach and N. Peleties, *Angew. Chem.*, **81**, 465 (1969); *Chem. Ber.*, **105**, 511 (1972).

A typical procedure for path A is as follows. The reaction was carried out on 21.4 g (0.1 mol) of methyl dodecanoate as described by Rathke[7] for the conversion of ethyl hexanoate to ethyl 2-iodohexanoate except that the solution of iodine in THF was replaced by a solution of 28.3 g (0.12 mol) of PhSeBr which was prepared by the addition of 9.60 g (0.06 mol) of bromine to 18.7 g (0.06) of diphenyl diselenide in THF. After the PhSeBr had been added to the enolate at −78°, the reaction mixture was stirred for 1 hr then allowed to warm to room temperature and poured into a cold aqueous solution of NH_4Cl and extracted with ethyl acetate, washed with 1 *N* HCl and $NaHCO_3$, dried, and filtered. To the resulting yellow solution was slowly added 30 ml (0.23 mol) of 40% (7.7 *M*) peracetic acid. The turbid white mixture was stirred at 23–25° for 2 hr, poured into cold (0°) water, washed with Na_2CO_3, $NaHSO_3$, and brine, dried, filtered, concentrated, and distilled to yield 17.6 g (83%) of (*E*)-methyl 2-dodecenoate, bp 89–91° (0.63 mm).

Following the above procedure exactly (0.1 mol scale) the unsaturated lactone **10** was obtained in 56% isolated yield [bp 93–95° (0.9 mm)] from the corresponding saturated γ-lactone.



10



11

With several modifications, procedure A has enabled us to effect the first synthesis of the recently isolated[10] pollen attractant (**11**) of foraging honey bees. The enolate of methyl linoleate was prepared as described in procedure A, then 1.2 equiv of diphenyl diselenide was added in place of phenylselenenyl bromide.[11] After the reaction mixture had warmed to room temperature, ~3 equiv of sodium periodate (dissolved in aqueous methanol) was added as the oxidant instead of the peracid or hydrogen peroxide usually employed. The methyl ester of octadeca-(*E*,2*Z*,*Z*)-9,12-trienoic acid (**11**) was isolated (preparative tlc) in 80% yield. Its ir, nmr, and uv spectra were identical with those published for the methyl ester of the natural substance.

These new procedures for the synthesis of α,β-unsaturated carbonyl compounds should often prove superior to those previously available.

Acknowledgment. We thank Crist Filer for donating a sample of 4-acetoxycyclohexanone. One of us (K. B. S.) is grateful to Professor Hans J. Reich (Wisconsin) for communicating unpublished results similar to ours. Reich and coworkers have observed that ketone enolates as well as ester enolates react with PhSeBr to give after oxidation the unsaturated carbonyl compounds. We thank the National Science Foundation (GP-30485X), Hoffmann-La Roche Inc., the Mobil Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support.

(10) C. Y. Hopkins, A. W. Jevans, and R. Boch, *Can. J. Biochem.*, **47**, 433 (1969).

(11) The use of PhSeBr in this case gave poor yields presumably because it readily adds to olefins. We shall soon report on the synthetic utility of processes which begin with the addition of ArSeX reagents to olefins.

(12) National Institutes of Health Predoctoral Fellow, 1969–1973.

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Hydrogen–Deuterium Exchange Kinetics of the C-2 Protons of Imidazole and Histidine Compounds[1]

Sir:

The kinetics of the deuteration at the 2 position in imidazole and some substituted imidazoles has been studied by various workers.[2–5] The mechanism proposed for the reaction involves the interaction of the protonated form of the imidazole with OD^- or D_2O, with replacement of the proton at the 2 position by a negative charge to produce an ylide (slow step). The second, fast step, involves reaction of the ylide with D_2O, with substitution of deuterium at the 2 position.[5] We have been concerned with the determination of the p*K* values[6–8] and the kinetics of the deuteration of histidine residues in proteins.[9] In this communication we report on the kinetics of the deuteration of various substituted imidazole and histidine compounds, which serve as suitable model compounds for the exchange behavior in proteins.

The purities of the various model compounds shown in Table I were checked by pmr spectroscopy. The

Table I

Compound	Apparent dissociation constants[a] pK_1	pK_2	pK_3	$k_1 \times 10^{-3}$, l. mol^{-1} min^{-1}	$k_2 \times 10^{-3}$, l. mol^{-1} min^{-1}
Imidazole		7.6			6.4[b]
Imidazole acetic acid		7.7			2.9[c]
N-Acetyl-L-histidine		7.6			3.1[b]
L-Histidine	6.6	7.6	9.6	14.4[b]	2.8[b]
Histamine	6.4	7.5	10.0	24[c]	4.2[c]
Glycyl-L-histidine	7.2	7.6	10.0	5.0[c]	3.1[c]
β-Alanyl-L-histidine	7.4	7.6	10.0	4.6[b]	3.7[b]

[a] K_1, K_2, and K_3 are defined by the equations $N^+D_3Im^+DCOO^- \rightleftharpoons N^+D_3ImCOO^- + D^+$ (K_1), $ND_2Im^+DCOO^- \rightleftharpoons ND_2ImCOO^- + D^+$ (K_2), and $N^+D_3ImCOO^- \rightleftharpoons ND_2ImCOO^- + D^+$ (K_3) where the structures are defined in the text. A detailed discussion of the origin of these values is given elsewhere.[10] [b] At 37°. [c] At 35°.

(1) Financial support by the Australian Research Grants Committee is gratefully acknowledged.

(2) H. S. Staab, *Tetrahedron Lett.*, 845 (1964).

(3) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, **86**, 1865 (1964).

(4) T. M. Harris and J. C. Randall, *Chem. Ind. (London)*, 1728 (1965).

(5) J. D. Vaughan, Z. Mughrabi, and E. C. Wu, *J. Org. Chem.*, **35**, 1141 (1970).

(6) J. H. Bradbury and H. A. Scheraga, *J. Amer. Chem. Soc.*, **88**, 4240 (1966).

(7) J. H. Bradbury and P. Wilairat, *Biochem. Biophys. Res. Commun.*, **29**, 84 (1967).

(8) N. L. R. King and J. H. Bradbury, *Nature (London)*, **229**, 404 (1971).

(9) J. H. Bradbury and B. E. Chapman, *Biochem. Biophys. Res. Commun.*, **49**, 891 (1972).