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Phenyl Selenide Anion, a Superior Reagent for the S_N2 Cleavage of Esters and Lactones

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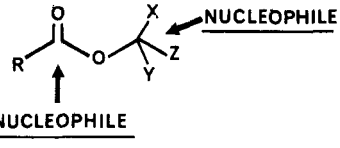
The scope and limitations of S_N2-type cleavages of esters and lactones with phenyl selenide anion are discussed. The reagent, when generated properly, is found to be an extremely potent nucleophile. However, its nucleophilicity can be greatly attenuated by varying the counterion and/or the degree of solvation of the anion. The reagent can be used in the presence of a variety of functional groups and exhibits a high degree of selectivity; e.g., methyl esters are selectively cleaved in the presence of ethyl esters. As the hindrance around the carbinol carbon increases, products derived from acyl oxygen cleavage are observed. The mechanistic implications of this are discussed.

Ester hydrolyses are among the simplest and most common of all laboratory reactions and are easily accomplished by heating the compound in either aqueous acid or base. However, there are many situations in which it is either necessary or desirable to avoid exposing a particular substrate to strongly acidic or basic solutions. In these circumstances the alternative approach of cleaving esters via nucleophilic attack at the carbinol carbon can be employed. However, since these nucleophilic cleavage reactions are S_N2 processes, they are quite sensitive to steric hindrance at the site of attack and have typically been successful only with methyl esters.[2]



In attempting to optimize conditions used in S_N2-type ester cleavage reactions, we speculated that the single most important factor would appear to be the choice of the nucleophile employed in the reaction. Since an ester has two sites which can be potentially attacked by a nucleophile, one should choose a nucleophile which either exhibits a preference for attack at the carbinol carbon or which attacks the carbonyl carbon reversibly and the carbinol carbon irreversibly.

Using the principles of hard soft acid base theory, soft nucleophiles are predicted to show a preference for attack on the carbinol carbon (soft–soft interaction) rather than the carbonyl carbon (soft–hard interaction). In evaluating the various soft nucleophiles which are available, phenyl selenide anion, a priori, would appear to be the best choice because (a) its inherently low ionization potential and high polarizability should combine to make it an extremely potent nucleophile, (b) it is an extremely weak base, (c) it is very easily generated, and (d) it is a relatively poor leaving group.

In 1977 we reported preliminary details of our studies on the applicability of phenyl selenide anion to S_N2-type cleavages of esters[3] and lactones.[4,5] In this paper we provide additional insight into (a) the selectivity of the reagent in the presence of a variety of functional groups, (b) the effect of varying the counterion and/or the degree of solvation on the nucleophilic reactivity of the anion, and (c) the scope and limitations of this method, relative to the other ester alkyl–oxygen cleavage processes in the literature. On the basis of the results reported here, it is our belief that *phenyl selenide anion is overall the most effective reagent yet reported for carrying out S_N2-type ester cleavage reactions.*

Generation of Phenyl Selenide Anion

The standard conditions used for generating phenyl selenide anion typically involve reduction of diphenyl diselenide with sodium borohydride in ethanol/THF, according to the method of Sharpless[6] (eq 1). Under these

$$\mathrm{PhSeSePh} + 2\mathrm{NaBH_4} \xrightarrow[\mathrm{EtOH}]{\mathrm{THF}} 2\mathrm{NaSePh} + 2\text{“}\mathrm{BH_3}\text{”} + \mathrm{H_2} \quad (1)$$

(1) Fellow of the Alfred P. Sloan Foundation, 1980–1984.
(2) The S_N2-type cleavage of esters is the subject of a recent review, see: McMurry, J. *Org. React.* **1977**, *24*, 187.
(3) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365.
(4) Liotta, D.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4369.
(5) See also: (a) Scarborough, R.; Smith, A. B. *Tetrahedron Lett.* **1977**, 4361; (b) Gunther, W. H. *J. Org. Chem.* **1966**, *31*, 1202; (c) Sundelar, K.; Metysova, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3801; (d) Agenas, L.-B. *Ark. Kemi* **1965**, *24*, 415.

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$$PhSeSePh + 2Na^{\circ} \xrightarrow{THF} 2NaSePh \quad (2)$$

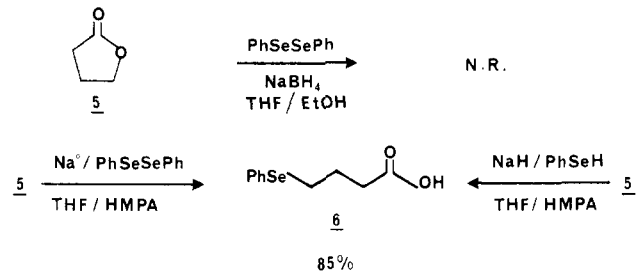
$$PhSeH + NaH \xrightarrow{THF} NaSePh + H_2 \quad (3)$$

conditions a clear, colorless and homogeneous solution of the anion is produced. If 1 molar equiv of *n*-decyl bromide (**1**) is added to the solution, one obtains a 90% yield of *n*-decyl phenyl selenide (**2**) after a standard workup. However, if one attempts to generate phenyl selenide anion by reaction of diphenyl diselenide with sodium metal in dry refluxing THF, one observes the formation of a copious precipitate over the period of 3–4 h (eq 2). Moreover, a precipitate, whose chemical and physical properties in every way resemble the precipitate generated according to eq 2, can also be formed by reaction of benzeneselenol and sodium hydride in THF at room temperature (eq 3). When the precipitate, generated either according to eq 2 or 3, is solubilized by the addition of a small amount of hexamethylphosphoramide (HMPA) and 1 molar equiv of *n*-decyl bromide is added to the resulting solution at room temperature, a quantitative yield of **2** is obtained after a standard workup. Thus, although both methods ultimately yield the same product, the anions which are involved in these reactions are obviously quite different.

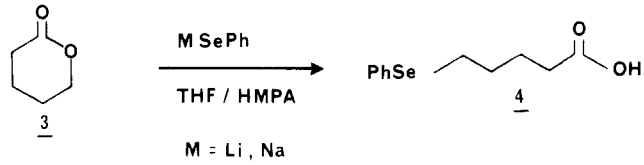
Some insight into the differences between the process given by eq 1 and those given by eq 2 and 3 can be obtained by examining the stoichiometry of the reactions. Besides the hydrogen evolved in eq 1 and 3, the only difference in the products of these reactions is the presence of 2 equiv of "BH_3" in eq 1. Since it is known that in borohydride reductions the hydrides are replaced by alkoxy groups derived from the alcohol solvent,[8] it is reasonable to assume that in the case of eq 1, the soft acid "BH_3" preferentially interacts with the soft base, phenyl selenide anion, rather than the harder alcohol solvent. Thus, the stoichiometry, as written in eq 2, implies that *the reduction of diphenyl diselenide with sodium borohydride generates a phenyl selenide–borane complex*. Consistent with this, we have found that the addition of both absolute ethanol and diborane in THF to a reaction mixture, generated according to either eq 2 or 3, immediately dissolves the precipitate and forms a clear, colorless, and homogeneous solution, which in every respect resembles the solution generated according to eq 1.[9] Upon addition of 1 molar equiv of **1**, **2** is again obtained in 93% yield.

Since phenyl selenide anion, generated according to either eq 2 or 3, is not a complex, it should be substantially more reactive than the anion generated according to eq 1. In accord with this, exposure of a number of esters and lactones to the anion derived from sodium borohydride reduction of diphenyl diselenide leads to a quantitative recovery of the starting material. On the other hand, treatment of a wide variety of esters and lactones with the uncomplexed anion (eq 2 or 3) in THF/HMPA results in facile alkyl–oxygen cleavage reactions from which the corresponding carboxylic acids can be isolated in high overall yield (vide infra).

A less striking, but nonetheless significant, attenuation of the reactivity of phenyl selenide anion can be achieved by varying the counterion and/or the relative degree of



solvation of the ion pair. For example, when valerolactone (**3**) is allowed to reflux with sodium phenyl selenide in THF/HMPA for 3 h, one obtains an 85% yield of the ω-phenylselenenyl carboxylic acid **4**. When lithium is



substituted for sodium and the remainder of the reaction conditions are held constant, one only isolates a 33% yield of **4**. Thus, the more ionic sodium species is significantly more reactive than its lithium counterpart and therefore should be used in cases which require a powerful nucleophile. On the other hand, lithium phenyl selenide in many cases is an attractive reagent to use because (a) it is easily generated by reaction of benzeneselenol with an alkyllithium and (b) it is soluble in both ether and THF. While this species in the absence of HMPA is not sufficiently nucleophilic to effect ester cleavage reactions, it has proven to be quite convenient for carrying out many other less demanding nucleophilic displacement reactions.[10]

That the degree of solvation of the ion pair has a significant impact on its relative reactivity can be readily ascertained from the results of the following experiments. If butyrolactone (**5**) is allowed to react with sodium phenyl selenide in THF/HMPA, it requires 3 h at reflux to ultimately obtain an 85% yield of **6**. However, if one replaces the HMPA with 0.05 molar equiv of 18-crown-6, the same yield of product can be obtained by simply allowing the reaction mixture to stir for 3 h at room temperature. Thus, the combination of sodium phenyl selenide/18-crown-6/THF is at least an order of magnitude more reactive than the quite reactive combination of sodium phenyl selenide/HMPA/THF.

On the basis of our results we therefore propose the following reactivity gradient for phenyl selenide anion: NaSePh/18-C-6/THF > NaSePh/HMPA/THF > LiSePh/HMPA/THF > LiSePh/THF ≈ LiSePh/ether ≈ PhSeSePh/$NaBH_4$/THF/EtOH.

Synthetic Applications

The results of our study on the synthetic utility of phenyl selenide induced cleavages of esters and lactones are given in Table I.[11] Upon exposure to phenyl selenide anion, methyl esters undergo facile alkyl–oxygen cleavage reactions, irrespective of how hindered the ester is. This is best illustrated in the reactions of phenyl selenide anion with the series **38**, **7**, and **11**. In this series high yields of cleavage products are obtained, despite a large increase in the relative degree of steric hindrance around the ester.

(6) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. (b) Sharpless, K. B., Lauer, R. F.; Teranishi, A. Y. *Ibid.* **1973**, *95*, 6137.

(7) Adjustment of the solvent conditions to exactly match those used in the Sharpless procedure fails to dissolve the precipitate. In fact, even 10 times the quantity of ethanol used in ref 6 will not dissolve the precipitate. The precipitate, however, is soluble in pure, anhydrous ethanol.

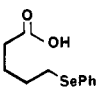
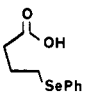
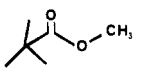
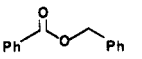
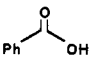
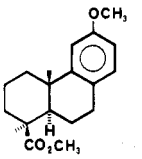
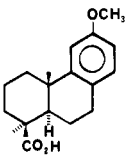
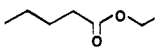
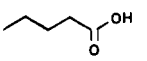
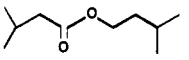
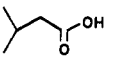
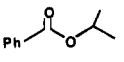
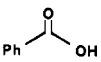
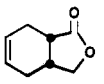
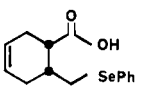
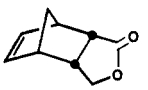
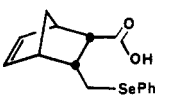
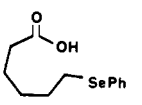
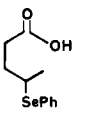
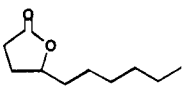
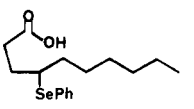
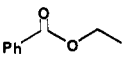
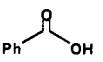
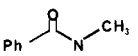
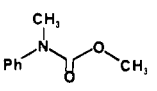
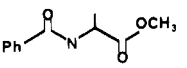
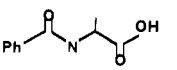
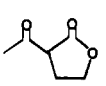
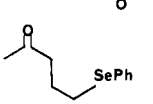
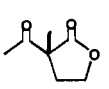
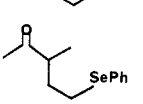
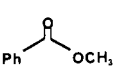
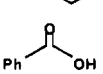
(8) Wigfield, D. C.; Gowland, F. W. *Tetrahedron Lett.* **1976**, 3373.

(9) The quantities of reagents were chosen to mimic the stoichiometry given in eq 1.

(10) For example, see: Zima, G.; Barnum, C.; Liotta, D. *J. Org. Chem.* **1980**, *45*, 2736.

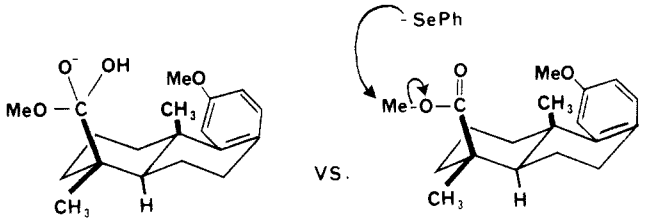
(11) All of the reactions listed in Table I were performed by using NaSePh/THF/HMPA, generated according to eq 3.

Table I

substr	substr no.	product[a]	product no.	time,[c] h	% isolated yield
	3		4	3	85
	5		6	3	85
	7		8	6	98
	9		10	8	96
	11		12	10	100
	13		14	10	99
	15		16	12	92
	17		10	96	92
	18		19	4	75
	20		21	4	80
	22		23	14	20
	24		25	55	96
	26		27	72	20
	28		10	18	99
	29			24	0
	30	Ph - NH - CH_3	31	10	93
	32		33	10	94
	34		35	4	99
	36		37	48[b]	94
	38		10	3	98

[a] Products were identified by analysis of their UV, NMR, and mass spectra, as well as by comparison of their physical properties with those of authentic samples. [b] This reaction time has not been optimized. [c] All reactions listed in this table were performed in HMPA/THF.[24]

This is particularly significant with regard to **11**, since under normal saponification conditions it is relatively unreactive. This sluggish reactivity toward aqueous base presumably results from the severe steric interactions which develop between the angular methyl group and the tetrahedral intermediate which forms upon attack of hydroxide anion (vide infra). By contrast, in the S_N2 cleavage of **11**, the carboxylate leaving group remains trigonal throughout the reaction. Therefore, since no "new" steric interactions develop during the S_N2 transition state, the reaction proceeds smoothly. Since in sterically hindered esters the carbinol carbon is virtually always less hindered than the carbonyl carbon, the phenyl selenide induced S_N2 cleavage of hindered methyl esters represents an attractive synthetic alternative to acid- or base-catalyzed hydrolyses.



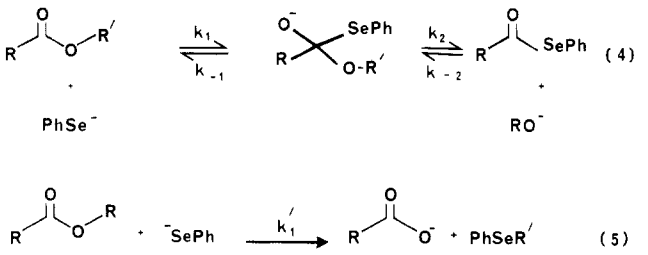
According to the literature, S_N2-type ester cleavage reactions which employ nucleophiles such as halides, amines, cyanide, potassium *tert*-butoxide, or thiocyanates usually work well only with methyl esters.[2,12] By contrast, phenyl selenide anion reacts cleanly and in high yield with a wide variety of more heavily substituted esters and lactones. Thus, benzyl, isoamyl and even isopropyl esters react with phenyl selenide anion to give their corresponding acids in nearly quantitative yields.

Not surprisingly, as the substitution pattern at or near the carbinol carbon increases, the rate of the alkyl–oxygen cleavage process decreases. In fact, this rate differential can, in certain cases, be exploited to allow for the selective cleavage of a methyl ester in the presence of an ester of a higher alcohol. For example, if 1.1 equiv of a 1:1 mixture of methyl benzoate (**38**) and ethyl benzoate (**28**) is allowed to react with 1 molar equiv of phenyl selenide anion for 5 h, only methyl phenyl selenide, the cleavage product derived from **37**, is observed; no trace of ethyl phenyl selenide is detectable via NMR. Thus, for synthetic purposes, selective cleavage of methyl esters can under normal circumstances[13] be achieved by using phenyl selenide anion.

Amides (e.g., **29**) are completely inert to phenyl selenide anion. In accord with this, selective "hydrolysis" of the methyl esters of **32** is observed upon treatment with phenyl selenide anion for 10 h. Urethane (**30**) also undergoes ester cleavage and subsequent decarboxylation to give *N*-methylaniline (**31**) in excellent yield.

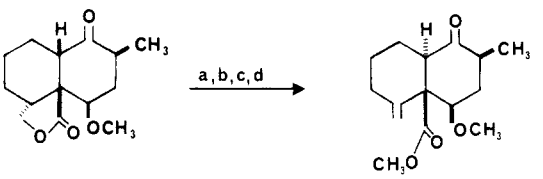
We have also examined the viability of phenyl selenide induced S_N2 cleavage reactions with substrates containing acidic protons. In principle, if a substrate is capable of transferring a proton to the nucleophilic cleavage reagent, the progress of the cleavage reaction could be drastically slowed or even effectively halted. This is apparently not an important problem when dealing with a relatively nonbasic nucleophile like phenyl selenide anion, as is evident in the conversion of **34** to **35** which proceeds at a rate comparable to the conversions of **3** to **4** and **5** to **6**.

Scheme I



The conversion of lactones to ω-phenylselenenyl carboxylic acids proceeds in a more or less similar fashion to the ester cleavage reactions discussed above. However, some differences do exist. For example, phenyl selenide anion reacts with caprolactone (**22**) at a rate which is substantially slower than **3** or **5**, despite the fact that each of the systems is the lactone of a primary carbinol. Thus, in addition to the normal consideration involving the degree of substitution at the carbinol center in esters, one must also take into account any conformational factors which effect the desired 180° trajectory of the incoming nucleophile.[14]

Finally, it should be noted that ω-phenylselenenyl carboxylic acids are, in general, useful synthetic precursors of ω-vinyl carboxylic acids.[4,5a,15] Perhaps the best illustration of this comes from the work of Goldsmith and John in which they were able to convert **39** to **40** in 73% overall yield using the methodology described here.[16] It should be noted that neither the ketone[17] nor the methyl ether[18] is adversely effected in this reaction sequence.



a. NaSePh/THF/HMPA; b. CH_2N_2, Et_2O; c. O_3, CH_2Cl_2, -78°C; d. Et_2NH, CH_2CL_2

Mechanism

It is our belief that on the basis of the mechanism illustrated in Scheme I, one can adequately rationalize all of the experimental observations reported here. Rather than phenyl selenide anion exclusively attacking esters at the carbinol carbon, it is more reasonable to assume that the S_N2 reaction (eq 5) competes with acyl oxygen cleavage

(12) Bartlett and Johnson have shown that lithium thiopropoxide in HMPA is an effective reagent for cleaving hindered methyl esters. See: Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459. We believe that this reagent, although effective, is less convenient than phenyl selenide anion because (a) standard solutions of the thiolate must be carefully prepared and protected from oxygen, and (b) isolation of many products from pure HMPA (vs. in our case, 3–5% HMPA in THF) can be tedious. At present, we have no data from which one can directly compare the nucleophilicity of the Bartlett–Johnson reagent, relative to our own reagent. For examples of ester cleavage reactions using lithium thiomethoxide, see: Kelly, T. R.; Dali, H. M.; Tsang, W. *Tetrahedron Lett.* **1977**, 3859.

(13) Clearly, in the extreme case in which a substrate contains a very hindered methyl ester and a relatively unhindered ethyl ester, complete selectivity may not be observed.

(14) Presumably, the preferred conformation of the seven-membered-ring lactones is less suitable for S_N2 displacement than their five- and six-membered-ring counterparts.

(15) Hoye et al. have recently used the S_N2 cleavage of a lactone by phenyl selenide anion as a key step in their synthesis of ancistrofuran. For preliminary details of the lactone ring opening step, see: Hoye, T. R.; Caruso, A. J. *Tetrahedron Lett.* **1978**, 4611.

(16) Goldsmith, D. J., Emory University, personal communication. We thank Professor Goldsmith for allowing us to report these preliminary details of his work.

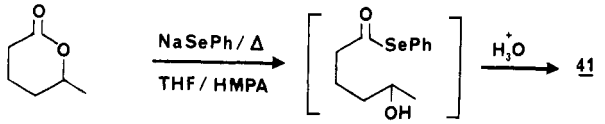
(17) Epimerization of the ring-juncture proton apparently occurs during the selenoxide elimination reaction (step d).

(18) Even aromatic methyl ethers are inert to phenyl selenide anion, as is illustrated in the conversions of **11** and **12**.

(eq 4). However, because the acyl–oxygen cleavage process produces a very reactive seleno ester,[19] the entire process is highly reversible. By contrast, it is likely that the S_N2 process is irreversible, since (a) the carboxylate anion produced is many orders of magnitude less nucleophilic than phenyl selenide anion and (b) phenyl selenide anion is a relatively poor leaving group.[20]

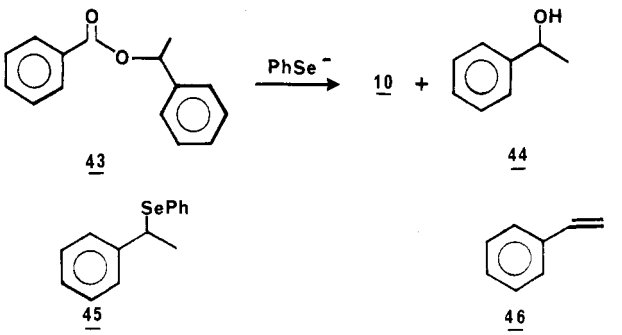
Some support for this mechanism is obtained from the following observations. First, in all conversions listed in Table I except the conversion of **17** to **10**, the related alkyl phenyl selenide is isolated in essentially quantitative yield as a byproduct.[21] In the case of **17** all attempts to observe even trace quantities of isopropyl phenyl selenide failed. Since, in principle, **10** could possibly form via an elimination reaction, attempts were made to trap any propene produced. These also failed. Our assumption is that **17** undergoes an acyl–oxygen cleavage and that the byproduct, 2-propanol, is lost during the aqueous workup.

Consistent with this, despite the fact that **41** is ultimately recovered unchanged after prolonged refluxing with phenyl selenide anion in THF/HMPA, a copious precipitate is observed to form as the reaction mixture heats. Careful filtration of the precipitate leads to a solid which upon treatment with aqueous acid and subsequent workup yields **41**. This observation is completely consistent with a situation in which for steric reasons acyl–oxygen cleavage becomes the dominant process. Thus, **42** is presumably produced and then reconverted back to **41** with acid.[22] Obviously, this observation is also not compatible with an elimination mechanism.



The mechanism depicted in Scheme I is also quite useful in understanding why lactones undergo S_N2 cleavage at a substantially faster rate than similarly substituted esters. While in some special cases ring strain may be important, the major difference between esters and lactones here is that for lactones the reaction of alkoxide with the seleno ester is an intramolecular process, whereas for esters it is intermolecular. Since the intramolecular process is presumably much faster than a similar intermolecular process, the equilibrium should, on a relative basis, be further to the left with lactones. As a consequence, at any given time there should be a relatively higher concentration of lactone, which would necessarily result in a faster overall reaction.[23]

The strongest evidence for competitive acyl–oxygen and alkyl–oxygen cleavage reactions comes from the reaction of **43** with phenyl selenide anions in refluxing THF for 24 h. Upon workup, one isolates benzoic acid (**10**), starting ester **43** and alcohol **44**. No traces of either selenide **45** or styrene (**46**) are observed. It thus appears quite likely



that the phenyl selenide induced cleavage of hindered alkyl esters proceeds by an acyl–oxygen cleavage, followed by a subsequent hydrolysis of the resulting selenoester.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover Uni-Melt capillary melting point apparatus. Infrared spectra were determined with Perkin-Elmer Model 257, 457, and 727 spectrophotometers. Nuclear magnetic resonance spectra were recorded by using Varian T-60, EM-360, and EM-390 spectrometers, and chemical shifts are reported in parts per million (δ) relative to an internal tetramethylsilane reference. Normal mass spectra were recorded by using a Finnigan 4000 GC-MS system and a Varian Associates M-66 spectrometer. Precise mass measurements were carried out with the Varian Associates M-66 spectrometer. Reagents and solvents were purified by standard methods.

General Procedure for the Conversion of Esters and Lactones with Phenyl Selenide Anion. This process is illustrated with methyl benzoate (**38**). To a dry, 25-mL, three-necked, round-bottomed flask containing a stirring bar, two serum caps, and a reflux condenser are added 10 mL of dry THF and 0.35 g (7.29 mmol, 2 equiv) of a 50% oil dispersion of NaH. The system is placed under a N_2 atmosphere, allowed to stir for approximately 2 min, and then allowed to settle for 5 min. The oil/THF mixture is removed by pipet and replaced by an additional 10 mL of dry THF. This procedure is repeated twice. At this point 15 mL of dry THF is added to the activated sodium hydride. The mixture is again stirred, and 1.15 g (7.32 mmol, 2 equiv) of benzeneselenol, 3.1 g (17.2 mmol, 2.4 equiv) of HMPA, and 0.50 g (3.67 mmol, 1 equiv) of **38** are carefully injected via syringe into the mixture. Care should be taken at this point, due to the exothermic nature of the benzeneselenol addition and to excessive foaming during the addition of HMPA. The reaction mixture is then allowed to heat at reflux temperature for 3 h. At the end of this period, the mixture is allowed to cool to room temperature, and the THF is stripped off under reduced pressure. The excess NaH is quenched with 10 mL of H_2O. The resulting basic solution is washed with three 50-mL portions of ethyl ether. This layer contains crude methyl phenyl selenide, which can be isolated by simply drying the solution ($MgSO_4$) and stripping the solvent. The aqueous layer is then acidified with 10% (3 N) HCl solution. The acidified layer is then washed three times with 30-mL portions of ethyl ether. The combined organic layers are dried over $MgSO_4$ and stripped of solvent to give 0.439 g (3.596 mmol, 98% yield) of benzoic acid (**10**). Further purification can be achieved by silica gel chromatography, when necessary.

Procedure for the Isolation of 35 and 37. The procedure is the same as in the general procedure given above except for certain steps in the workup. After the reaction mixture has cooled to room temperature, the excess NaH is quenched with 10 mL of H_2O, and the bulk of the THF is then stripped. The resulting basic solution is washed with four 50-mL portions of ether. The ether layers are then combined and washed with four 30-mL portions of 10% HCl solution. The organic layer is then dried over $MgSO_4$ and stripped of solvent to give the product.

Procedure for the Isolation of 31. The procedure is the same as in the general procedure given above except for certain steps in the workup. The mixture is allowed to come to room temperature, and the excess NaH is quenched with 10 mL of H_2O. The mixture is then washed with four 35-mL portions of ether. The combined organic layers are then washed three times with

(19) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2736.
(20) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.
(21) Carboxylic acid/alkyl phenyl selenide mixtures are readily separated by performing multiple ether extractions of basic aqueous solutions of the mixture.
(22) A similar process may be partially occurring in the conversion of **26** to **27**.
(23) A second complementary factor which probably plays a role in relative reactivity of lactones and esters is the unfavorable dipole–dipole interactions which are known to be present in lactones. This interaction is, of course, eliminated after ring opening.
(24) Although the combination of NaSePh/18-crown-6/THF is substantially more reactive than NaSePh/HMPA/THF, it is sometimes less convenient to use due to the formation of emulsions during workup.

25-mL portions of H_2O. The ether layer is then dried over $MgSO_4$ and stripped of solvent. The resulting mixture is then separated by silica gel chromatography by first eluting with hexane to remove the methyl phenyl selenide and then with 1:1 ether/hexane to remove the product. The combined ether/hexane solutions are dried over $MgSO_4$ and stripped of solvent to give **31**.

Physical and Spectral Data. For **4**: mp 56–58 °C; ^{1}H NMR ($CDCl_3$) 10.50–9.90 (br s, 1), 7.70–7.12 (m, 5), 3.10–270 (t, J = 6 Hz, 2), 2.52–2.13 (t, J = 6 Hz, 2), 2.01–1.60 (m, 4); IR ($CHCl_3$) 1700 cm^{-1}; mass spectrum, m/e 256, 258; precise mass calcd for $C_{11}H_{14}O_2{}^{78}Se$ m/e 256.016 65, found 256.023 62.

For **6**: yellow oil; ^{1}H NMR ($CDCl_3$) 10.37–10.10 (br s, 1), 7.70–7.12 (m, 5), 3.12–2.83 (t, J = 7 Hz, 2), 2.64–2.40 (t, J = 6 Hz, 2), 2.27–1.84 (m, 2); IR ($CHCl_3$) 1705 cm^{-1}; mass spectrum, m/e 242, 244; precise mass calcd for $C_{10}H_{12}O_2{}^{80}Se$ m/e 244.000 20, found 244.000 38.

For **8**: colorless liquid; ^{1}H NMR ($CDCl_3$) 1.20 (s, 9), 9.47 (br s, 1).

For **10**: mp 120–121 °C; ^{1}H NMR ($CDCl_3$) 10.50–10.11 (br s, 1), 8.27–7.40 (m, 5).

For **12**: mp 157–158 °C; ^{1}H NMR ($CDCl_3$) 7.08–6.47 (m, 3), 3.75 (s, 3), 2.94–1.52 (m, 11), 1.66 (s, 3), 1.13 (s, 3).

For **14**: colorless liquid; ^{1}H NMR ($CDCl_3$) 11.00 (br s, 1), 2.54–2.20 (t, J = 6 Hz, 2), 1.94–1.15 (m, 4), 1.10–0.78 (t, J = 6 Hz, 3).

For **16**: colorless liquid; ^{1}H NMR ($CDCl_3$) 9.52 (br s, 1), 2.40–1.82 (m, 3), 1.13–0.88 (d, J = 6 Hz, 6).

For **19**: yellow oil; ^{1}H NMR ($CDCl_3$) 10.41 (br s, 1), 7.70–7.10 (m, 5), 5.86–5.42 (br s, 2), 3.00–2.90 (m, 2), 2.40–2.01 (m, 5), 1.45–1.25 (m, 1); IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 294, 296; precise mass calcd for $C_{14}H_{16}O_2{}^{80}Se$ m/e 296.031 52, found 296.031 40.

For **21**: yellow oil; ^{1}H NMR ($CDCl_3$) 10.30 (br s, 1), 7.70–7.12 (m, 5), 6.40–5.90 (m, 2), 3.20–2.91 (m, 4), 2.11–2.02 (m, 1), 1.43–1.11 (m, 3); IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 308, 310; precise mass calcd for $C_{15}H_{18}O_2{}^{80}Se$ m/e 310.047 17, found 310.047 03.

For **23**: mp 44–46 °C; ^{1}H NMR ($CDCl_3$) 10.05 (br s, 1), 3.08–2.92 (t, J = 6 Hz, 2), 2.06–1.41 (m, 6); IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 270, 272; precise mass calcd for $C_{12}H_{16}O_2{}^{80}Se$ m/e 272.031 52, found 272.036 49.

For **25**: mp 48–51 °C; ^{1}H NMR ($CDCl_3$) 10.20 (br s, 1), 3.58–3.16 (m, 1), 2.80–2.42 (t, J = 7 Hz, 2), 2.14–2.71 (m, 2), 1.60–1.40 (d, J = 7 Hz, 3), 7.70–7.12 (m, 5); IR 1705 cm^{-1}; mass spectrum, m/e 256, 258; precise mass calcd for $C_{11}H_{14}O_2{}^{80}Se$ m/e 258.015 85, found 258.020 03.

For **27**: yellow oil; ^{1}H NMR ($CDCl_3$) 10.23 (br s, 1), 7.65–7.00 (m, 5), 3.31–2.93 (m, 1), 2.71–2.35 (m, 2), 2.03–0.80 (m, 15); IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 326, 328; precise mass calcd for $C_{16}H_{24}O_2{}^{80}Se$ m/e 328.094 12, found 328.097 36.

For **31**: colorless liquid; ^{1}H NMR ($CDCl_3$) 7.34–6.28 (m, 5), 3.50 (br s, 1), 2.71 (s, 3).

For **33**: mp 143–145 °C; ^{1}H NMR (Me_2SO-d_6 + $CDCl_3$) 10.05 (br s, 1), 8.03–7.27 (m, 6), 5.00–4.40 (overlapping dq, $J^1 = J^2$ = 7 Hz, 1), 1.65–1.40 (d, J = 7 Hz, 3).

For **35**: yellow oil; ^{1}H NMR ($CDCl_3$) 7.63–7.00 (m, 5), 3.04–2.80 (t, J = 7 Hz, 2), 2.70–2.40 (t, J = 6 Hz, 2), 2.20–1.77 (m with overlapping s, 5); IR ($CHCl_3$) 1708 cm^{-1}; mass spectrum, m/e 240, 242; precise mass calcd for $C_{11}H_{14}O^{80}Se$ m/e 242.020 96, found 242.019 48.

For **37**: yellow oil; ^{1}H NMR ($CDCl_3$) 7.60–7.15 (m, 5), 3.02–2.80 (t, J = 7 Hz, 2), 2.27–1.60 (m with overlapping s, 6); IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 254, 256; precise mass calcd for $C_{12}H_{16}O^{80}Se$ 256.036 61, found 256.043 72.

For **44**: colorless liquid; ^{1}H NMR ($CDCl_3$) 7.20 (br s, 5), 4.92–4.50 (q, J = 7 Hz, 1), 1.50–1.30 (d, J = 7 Hz, 3).

Acknowledgment. Financial support for this work was provided by grants from the National Institutes of Health and Research Corp.

Registry No. **1**, 112-29-8; **2**, 61539-89-7; **3**, 542-28-9; **4**, 66241-82-5; **5**, 96-48-0; **6**, 23768-06-1; **7**, 598-98-1; **9**, 120-51-4; **11**, 1231-74-9; **13**, 539-82-2; **15**, 659-70-1; **17**, 939-48-0; **18**, 2744-05-0; **19**, 77461-93-9; **20**, 64550-47-6; **21**, 77461-94-0; **22**, 502-44-3; **23**, 66241-83-6; **24**, 108-29-2; **52**, 66241-87-0; **26**, 706-14-9; **27**, 77461-95-1; **28**, 93-89-0; **29**, 613-93-4; **30**, 28685-60-1; **32**, 7244-67-9; **34**, 517-23-7; **35**, 66241-86-9; **36**, 1123-19-9; **37**, 77461-96-2; **38**, 93-58-3; phenyl selenide anion, 14971-39-2.

Deamination of Primary Aminoalkanols. Formation of Substituted *N*-Nitroso-1,3-oxazolidines and *N*-Nitroso-1,3-tetrahydrooxazines[1]

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The deamination of 2-amino- and 3-aminoalkanols in the presence of nitrous acid is reported. The 2-aminoalkanols generated aldehydes upon loss of nitrogen, followed by oxazolidine formation by reaction with starting material and finally nitrosation to substituted *N*-nitroso-1,3-oxazolidines. Ethanolamine gave *N*-nitroso-2-methyl-1,3-oxazolidine; 2-amino-2-methyl-1-propanol was converted to *N*-nitroso-2-isopropyl-4,4-dimethyl-1,3-oxazolidine. Deamination of 1-amino-2-propanol gave propionaldehyde, which upon further reaction produced *cis*- and *trans*-*N*-nitroso-2-ethyl-5-methyl-1,3-oxazolidines. (*E*)- and (*Z*)-*N*-nitroso-2-ethyl-4-methyl-1,3-oxazolidines were obtained from the deamination of 2-amino-1-propanol. Propionaldehyde and formaldehyde were produced by diazotiazation of 1-amino-3-propanol. Further reaction of the aldehydes with unreacted amine formed *N*-nitroso-1,3-tetrahydrooxazine and *N*-nitroso-2-ethyl-1,3-tetrahydrooxazine. Nuclear magnetic resonance and deuterium-exchange studies of these compounds are discussed.

It is well established that 2-amino- and 3-aminoalkanols can undergo a pinacolic rearrangement to aldehydes, ketones, epoxides and glycols in nitrous acid[2,3] (Scheme I). Howver, Nance et al.[4] were the first to isolate a nitrosooxazolidine from the deamination of 2-amino-1-butanol. The reaction involved the generation of butyraldehyde followed by oxazolidine formation with unreacted aminoalkanol and finally nitrosation to *N*-nitroso-2-propyl-4-ethyl-1,3-oxazolidine. When 3-aminoalkanols were deaminated, carbonyl compounds were produced,[3] but nitrosamine formation in these reaction has not been reported.

(1) Presented in part at the 15th Annual Middle Atlantic Regional Meeting of the American Chemistry Society at Washington, DC., Jan 7–9, 1981, No. ORGN 323.

(2) H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1324 (1939); P. I. Pollak and D. Y. Curtin, *ibid.*, **72**, 961 (1950); G. E. McCasland, *ibid.*, **73**, 2293 (1951).

(3) J. English, Jr., and A. D. Bliss, *J. Am. Chem. Soc.*, 78, 4057 (1956).

(4) H. R. Nance and M. H. Gollis *J. Am. Chem. Soc.*, **74**, 5189 (1952).

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