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A NOVEL SYNTHESIS OF THIOLACTONES: SELENOTHIOLACTONIZATION

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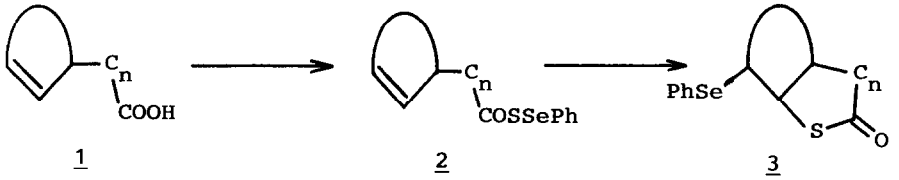
Abstract:Intramolecular cyclization of S-acyl phenylselenosulfides to selenothiolactones and subsequent oxidative removal of the phenylseleno group are described.

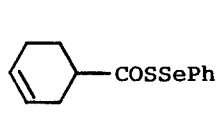
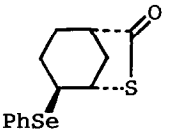
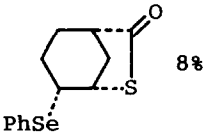
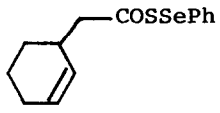
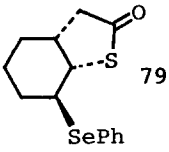
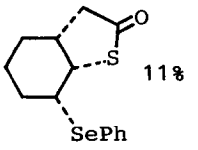
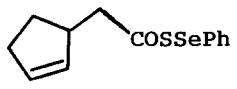
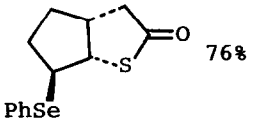
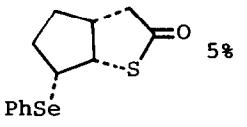
Organoseleno and organothio chemistry has received considerable attention in organic synthesis because of the easily manipulating nature of seleno and thio groups.[1] Previously we reported the convenient synthesis[2] of S-acyl phenylselenosulfides by the reaction of thiocarboxylic acids with N-phenylselenophthalimide (N-PSP) and the selenothiocarboxylation[3] of olefins by S-benzoyl phenylselenosulfide which offers a unique and useful method for simultaneous introduction of phenylseleno and thiocarboxy groups. In this communication we disclose a novel synthetic method for the thiolactone moiety which is of functionally importance not only for synthetic intermediates[4] but also for biological activities.[5]

N-PSP has been developed for selenocyclization such as selenolactonization of alkenoic acids.[6] We have now found that the reaction of thiocarboxylic acids containing a double bond with N-PSP smoothly proceeds to give the S-acyl phenylselenosulfides 2. No formation of selenothiolactones was observed at this stage. Successful cyclization could be achieved when the isolated S-acyl phenylselenosulfides 1 were heated at reflux in benzene with a small amount of AIBN. This new methodology, selenothiolactonization, is illustrated below.



1 2 3

Table 1. Selenothiolactonization of selenosulfide 2.

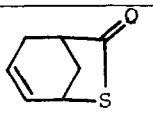
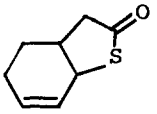
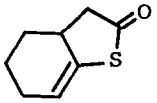
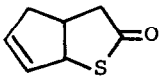
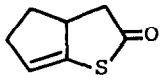
selenosulfide (yield*)	reaction time, hr	product, isolated yield	
	6	 85%	 8%
2a (90%)		trans-3a	cis-3a
	6	 79%	 11%
2b (81%)		trans-3b	cis-3b
	13	 76%	 5%
2c (80%)		trans-3c	cis-3c

* Yield based on the carboxylic acid 1.

In a typical experiment, to a CH_2Cl_2 (2 ml) solution of N-PSP(275 mg, 0.91 mmol) was added at -78° a CH_2Cl_2 (1 ml) solution of 3-cyclohexene-1-thiocarboxylic acid, prepared[7] from the carboxylic acid[8] 1a (95 mg, 0.76 mmol) via the acid chloride and used without purification, and the mixture was stirred for 0.5 hr. Hexane (10 ml) was added and the resultant precipitate was filtered. The filtrate was then evaporated and the residue was purified by flash chromatography (silica gel, hexane/AcOEt 99/1) giving selenosulfide 2a (203 mg, 90% yield from the acid 1a). Then a benzene (2.6 ml) solution of selenosulfide 2a (133 mg, 0.45 mmol) and AIBN (7.5 mg, 0.045 mmol) was refluxed under an argon atmosphere for 6 hr. Purification by flash chromatography (silica gel, hexane/AcOEt 100/1-7/3) gave trans-selenothiolactone trans-3a (112 mg, 85%) and cis-selenothiolactone cis-3a (11 mg, 8%).[9]

Selenosulfides 2b and 2c, prepared from acids 1b and 1c in high yields, also gave trans-selenothiolactones trans-3b and trans-3c as major products as shown in Table 1. The lack of stereospecificity shows a radical intermediate is involved in selenothiolactonization.[10]

Table 2. Oxidation of selenothiolactone 3.

selenothiolactone	product			
				
trans-3a	4a	100%		
cis-3a	4a	68%		
				
trans-3b	4b	36%	5b	52%
cis-3b	4b	79%		
				
trans-3c	4c	85%	5c	10%
cis-3c	4c	70%		

Selective oxidation of the phenylseleno group could be attained by m-CPBA (1.2 equiv.) in CH_2Cl_2 at -20° for 0.5 hr, where the thiolactone sulfur was not affected.[11] After the addition of pyridine (4 equiv.) at the same temperature, the mixture was allowed to warm to room temperature and then refluxed for 1-2 hr to effect PhSeOH elimination. The results are summarized in Table 2. The syn-nature of the PhSeOH elimination reasonably resulted in the exclusive formation of allyl thiolactones 4a, 4b, and 4c from the respective cis-selenothiolactones cis-3a, cis-3b, and cis-3c. The PhSeOH elimination of trans-selenothiolactone trans-3a, in which hydrogens cis to the phenylseleninyl group are present on both adjacent carbon atoms, led to the exclusive formation of allyl thiolactone 4a. The reaction of trans-3c also gave allyl thiolactone 4c as a major product. Noteworthy is the reaction of trans-3b which resulted in the predominant formation of vinyl thiolactone 5b.[12]

Selenothiolactonization offers a useful synthetic method of functionalized thiolactones. We are currently exploring further scope of the reaction.

References and notes

(1) H. J. Reich, Acc. Chem. Res., 12, 22 (1979); D. Liota, ibid., 17, 28 (1984); E. Vedejs and G. A. Krafft, Tetrahedron, 38, 2857 (1982).

(2) T. Toru, M. Nishigaki, T. Seko, T. Kanefusa, and E. Maekawa, Synthesis, 878 (1985).

(3) T. Toru, T. Seko, and E. Maekawa, Tetrahedron Lett., 26 , 3263 (1985).

(4) E. Vedejs, Acc. Chem. Res., 17, 358 (1984).

(5) C-L. J. Wang and J. M. Salvino, Tetrahedron Lett., 25, 5243 (1984) and ref. cited therein; D. H. Lucast and J. Wemple, Synthesis, 724 (1976).

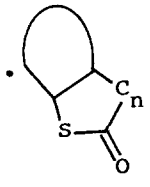
(6) K. C. Nicolaou, Tetrahedron, 37, 4097 (1981).

(7) P. Noble Jr. and D. S. Tarbell, Org. Syn., Vol. 4, 924, R. Norman Ed., Wiley, New York, 1963.

(8) H. O. House, R. G. Carlson, and H. Babad, J. Org. Chem., 28, 3359 (1968).

(9) The trans and cis isomers of selenolactones can be easily separated by chromatography. Rf values (Hexane/AcOEt 9/1):trans-3a, 0.36; cis-3a, 0.14; trans-3b, 0.26; cis-3b, 0.15; trans-3c, 0.25; cis-3c, 0.12. Selected spectral data are as follows: trans-3a, IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (1H, ddd, J=4.0, 3.7, 1.0 Hz, C<u>H</u>-S), 3.74 (1H, ddd, J=5.5, 3.7, 0.5 Hz, C<u>H</u>-Se): cis-3a, IR (neat) 1695 cm^{-1}; ^1H NMR (CCl_4) δ 3.98 (1H, m, C<u>H</u>-S), 3.50 (1H, ddd, J=9.8, 2.0, 2.0, C<u>H</u>-Se): trans-3b, IR (neat) 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (1H, dd, J=7.2, 5.1 Hz, C<u>H</u>-S), 3.46 (1H, ddd, J=7.2, 7.1, 3.7 Hz, C<u>H</u>-Se): cis-3b, IR (neat) 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.42 (1H, dd, J=4.4, 4.2 Hz, C<u>H</u>-S), 3,59 (1H, ddd, J=9.6, 6.8, 4.2 Hz, C<u>H</u>-Se): trans-3c, IR (neat) 1696 cm^{-1}; ^1H NMR (CCl_4) δ 4.15 (1H, dd, J=4.6, 2.6 Hz, C<u>H</u>-S), 3.78 (1H, ddd, J=6.4, 4.2, 2.6 Hz, C<u>H</u>-Se): cis-3c, IR (neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.57 (1H, ddd, J=6.2, 4.0, 1.2 Hz, C<u>H</u>-S), 3.85 (1H, m).

(10) The radical intermediacy was proven in the reaction of S-benzoyl phenylselenosulfide with an olefin, see ref. 3. Similarly the selenothiolactonization proceeds probably via a free radical pathway through an intermediate like a in which a rapid isomerization of the radical can take place. As to the conformational change of the radical intermediate, see F. W. Stacey and J. F. Harris, Jr., Organic Reactions,Vol. 13, 150, A. C. Cope, Ed., Wiley, New York, 1963.



a

(11) There are only a few examples of selective oxidation; for oxidation of the sulfide in seleno thioether, see K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, J. Am. Chem. Soc., 103, 3486 (1981), and for oxidation of a selenide containing 1,3-dithiane, see A. Nickon, A. D. Rodriguez, R. Ganguly, and V. Shirhatti, J. Org. Chem., 50, 2767 (1985).

(12) We have observed, in the oxidation of selenothiocarboxylation products, see ref. 3, a preference for elimination toward the carbon bearing the thiocarboxy group. The results will be reported in due course. No rearrangement of 4b and 4c to respective 5b and 5c was observed under the elimination conditions.

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