Reaction of PhSeCl or PhSCl with 2,3-Allenoic Acids: An Efficient Synthesis of β-Organoselenium or β-Organosulfur Substituted Butenolides

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Received 1 September 2003

Abstract: β-Organoselenium or β-organosulfur-substituted butenolides were prepared via the electrophilic cyclization of 2,3-allenoic acids with PhSeCl or PhSCl.

Key words: allenes, carboxylic acids, electrophilic cyclizations, selenium, sulfur, lactones

The history of organoselenium compounds can be dated back to 19th century. At that time, organoselenium had a reputation of being highly malodorous, unstable and unpleasant. The recognition of their toxic property and realization of selenium as an essential trace element in the diet prompted scientists to study the biological importance of organoselenium compound.[1] At present, organoseleuium has also been considered as important intermediates in organic synthesis.[1,2] On the other hand, butenolides are a class of compounds commonly observed in many natural and unnatural products with biological importance, which are considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, anti-inflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors, and phospholipase A_2 inhibitors, etc.[3] Butenolides are also important intermediates in organic synthesis due to the presence of the conjugated C=C bond as well as the five-membered lactone ring.[4] Thus, the development of efficient methods for the synthesis of β-organoselenium or β-organosulfur butenolides which combine the butenolide moiety with selenium is of current interest.[5] Recently, we have developed some methods for the efficient synthesis of differently substituted butenolides.[6–12] In this letter, we wish to disclose our recent results on the electrophilic cyclization of 2,3-allenoic acids with PhSeCl or PhSCl leading to β-organosulfur or β-organoselenium-substituted butenolides.[13]

We initiated this study with the cyclization of 2,3-octadienoic acid[14] and PhSeCl. When the reaction was carried out in CH_2Cl_2 at room tempearture the yield of **2a** was 47%[15] (entry 1, Table 1). With the notion that a molecule of HCl is generated during the reaction, we added a base such as *i*-Pr_2NEt, LiOAc, or Et_3N, however, the corresponding reaction in various solvents did not yield the product **2a** in any much better yields (entries 2–9, 11, and 13, Table 1). According to results in the screened solvents, MeCN was found to be the best. Thus, optimization of the reaction conditions was conducted in MeCN and finally it was found that when the reaction was carried out at 0 °C under N_2 in MeCN for 21 h, **2a** was isolated in 91% yield (entry 19, Table 1). It is necessary to carry out this reaction under N_2 since PhSeCl is sensitive to the moisture in air (compare entries 3 and 4, 5 and 6, 7 and 8, and 19, Table 1).

The cyclization of differently substituted 2,3-allenoic acids under these standard reaction conditions is summarized in Table 2.[16] From Table 2, it is obvious that 4-mono-substituted, 2,4-disubstituted, and 2,4,4-trisubstituted 2,3-allenoic acids can all be applied to afford β-phenylselenylbutenolides in 77–98% yields. Interestingly, this protocol can also be successfully applied to the corresponding electrophilic cyclization of PhSCl with 2,3-allenoic acids leading to β-phenylsulanylbutenolides (Table 3), which were previously prepared by the reaction of lithium 3-lithio-3-(phenylsulfanyl)-2-propenoates with aldehydes/ketones,[17] and Pd-catalyzed carbonylative cyclization of propargylic alcohols with disulfides or thiols.[18]

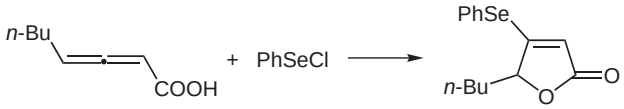
In conclusion, we have developed an efficient synthesis of β-phenylselanyl or phenylsulfanyl butenolides, which may have interesting biological importance due to the unique combination of selenium or sulfur with the butenolide moiety. Further investigation in this area is being pursued in our laboratory.

Acknowledgment

Financial support from the National Natural Science Foundation of China, the Major State Basic Research Development Program (Grant No. G2000077500), and Cheung Kong Scholar Programme are greatly appreciated. Shengming Ma is the recipient of 1999 Qiu Shi Award for Young Scientific Workers issued by Hong Kong Qiu Shi Foundation of Science and Technology (1999-2003) and jointly appointed by Zhejiang University and Shanghai Institute of Organic Chemistry. This work was conducted at Zhejiang University.

SYNLETT 2004, No. 1, pp 0085–0088
Advanced online publication: 4.12.2003
DOI: 10.1055/s-2003-43377; Art ID: U17303ST

Table 1 Cyclization of PhSeCl with 2,3-Octadienoic Acid



1a **2a**

Entry	PhSeCl (equiv)	Solvent	Additive (1 equiv)	N_2	T (°C)	Yield[a](%)
1	1.1	CH_2Cl_2	–	–	r.t.	47
2	1.2	CH_2Cl_2	$(i\text{-Pr})_2NEt$	–	r.t.	30
3	1.2	benzene	Et_3N	–	r.t.	11
4	1.2	benzene	Et_3N	N_2	r.t.	31
5	1.2	xylene	Et_3N	-	r.t.	47
6	1.2	xylene	Et_3N	N_2	r.t.	51
7	1.5	cyclohexane	Et_3N	-	r.t.	45
8	1.5	cyclohexane	Et_3N	N_2	r.t.	49
9	1.7	$CH_3CN–H_2O$ = 1:1	LiOAc	–	r.t.	16
10	1.5	$CH_3CN–H_2O$ = 1:1	–	–	r.t.	51
11	1.2	CH_3CN	Et_3N	–	r.t.	66
12	1.1	CH_3CN	–	–	r.t.	70
13	1.2	CH_3CN	$LiOAc{\cdot}2H_2O$	N_2	r.t.	58
14	1.5	CH_3CN	–	N_2	60	53
15	2.0	CH_3CN	–	N_2	–10	76
16	1.2	CH_3CN	–	N_2	r.t.	78
17	2.5	CH_3CN	–	N_2	r.t.	48
18	2.0	CH_3CN	–	N_2	0	49
19	1.5	CH_3CN	–	N_2	0	91

[a] Isolated yield.

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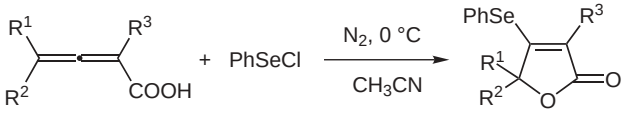
Table 2 Cyclization of PhSeCl with 2,3-Allenoic Acids[a]

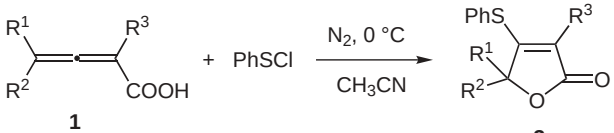


1 **2**

Entry	**1**			Time (h)	Isolated yield (%)
	R^1	R^2	R^3		
1	*n*-C_4H_9	H	H (**1a**)	19	91 (**2a**)
2	*n*-C_7H_{15}	H	H (**1b**)	14	92 (**2b**)
3	Ph	H	CH_3 (**1c**)	10.5	77 (**2c**)
4	Ph	H	*n*-C_3H_7 (**1d**)	10	98 (**2d**)
5	cyclohexyl	H	H (**1e**)	11	90 (**2e**)
6	Ph	H	Bn (**1f**)	10.5	84 (**2f**)
7	α-Naphthyl	H	*n*-C_3H_7 (**1g**)	7	98 (**2g**)
8	$(CH_2)_5$		CH_3 (**1h**)	8	94 (**2h**)

[a] The reaction was carried out using 0.2–0.4 mmol of 2,3-allenoic acid.

Table 3 Cyclization of PhSCl with 2,3-Allenoic Acids[a]



1 **3**

Entry	**1**			Time (h)	Isolated yield (%)
	R^1	R^2	R^3		
1	*n*-C_4H_9	H	H (**1a**)	9.5	49 (**3a**)
2	*n*-C_7H_{15}	H	H (**1b**)	10.5	71 (**3b**)
3	Ph	H	CH_3 (**1c**)	8	95 (**3c**)
4	cyclohexyl	H	H (**1e**)	9	77 (**3d**)
5	Ph	H	Bn (**1f**)	19.5	82 (**3e**)
6	$(CH_2)_5$		CH_3 (**1h**)	9	61 (**3f**)

[a] The reaction was carried out using 0.2–0.4 mmol of 2,3-allenoic acid.

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(16) **Typical Procedure for the Synthesis of 5-butyl-4-phenylselanyl-5*H*-furan-2-one (2a)**: To a solution of **1a** (41 mg, 0.3 mmol) in MeCN (1.5 mL) in a dry Schlenk tube was added PhSeCl (86 mg, 0.45 mmol) in MeCN (1.5 mL) at 0 °C under N_2 atmosphere. After the reaction was complete as monitored by TLC (eluent: petroleum ether–EtOAc, 8:1), the reaction mixture was evaporated and purified by flash chromatography on silica gel to give **2a** (79 mg, 91%) as a liquid. IR(neat): 1748, 1571 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.68–7.60 (m, 2 H), 7.50–7.34 (m, 3 H), 5.46 (d, *J* = 1.5 Hz, 1 H), 5.04 (ddd, J_1 = 1.5 Hz, J_2 = 3.5 Hz, J_3 = 7.7 Hz, 1 H), 1.98–1.85 (m, 1 H), 1.73–1.54 (m, 1 H), 1.53–1.23 (m, 4 H), 0.90 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 171.1, 169.7, 135.9, 130.2, 130.1, 124.5, 115.9, 84.2, 33.7, 26.00, 22.3, 13.8. MS (70 eV): *m*/*z* (%) = 296 (73.33) [M^+ (^{80}Se)], 239(100). Anal. Calcd for $C_{14}H_{16}O_2Se$: C, 56.97; H, 5.46. Found: C, 57.21; H, 5.70. All other new products were characterized similarly.

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