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Electrophilic Interaction of 2,3-Allenoates with PhSeCl. An Unexpected Highly Stereoselective Synthesis of 3-Phenylseleno-4-oxo-2(*E*)-alkenoates

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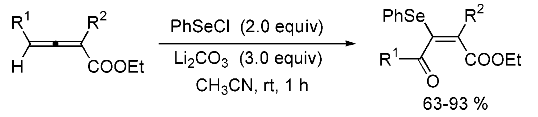
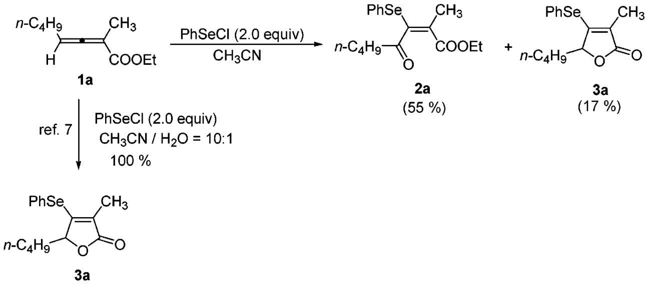


We have previously reported an efficient synthesis of β-phenylselenium-substituted butenolides via electrophilic cyclization of 2,3-allenoates with PhSeCl in aqueous MeCN. However, when 2,3-allenoates were treated with PhSeCl in MeCN, 3-phenylseleno-4-oxo-2(*E*)-alkenoates were formed unexpectedly. The addition of Li_2CO_3 improved the yield and the selectivity of the reaction. A possible mechanism involving a decomposition of selenate esters was proposed.

During the course of our systematic study on the chemistry of allenes,[1−3] interaction of allenes with electrophiles has also been recently explored.[4,5] Basically, we have demonstrated the electrophilic cyclization of 2,3-allenoates[4,6] and the halohydroxylation of sulfur- or selenium-substituted allenes.[5] It was also observed in this group that the electrophilic cyclization of 2,3-allenoates with PhSeCl afforded β-selenobutenolides.[7] In most cases, the reaction was conducted in aqueous MeCN to afford the butenolides in very high yields, especially for some 2,4-disubstituted 2,3-allenoates. However, it is interesting to observe that when the reaction was conducted in MeCN, an unexpected product, i.e., 3-phenylseleno-4-oxo-2(*E*)-alkenoate **2a**, was formed together with the butenolide **3a** (Scheme 1). These products containing important functional groups would be very useful intermediates in organic synthesis.[8] On the other hand, preparing different products from same starting material under different reaction conditions is of current interest in organic synthesis.[9] Herein, we report a highly stereoselective synthesis of 3-phenylseleno-4-oxo-2(*E*)-alkenoates from 2,3-allenoates by tuning the reaction parameters.

SCHEME 1



We tried to optimize the reaction conditions to get a useful selectivity for 3-phenylseleno-4-oxo-2(*E*)-alkenoates by studying the temperature and concentration effect. It should be noted that room temperature is the best and most convenient: when the temperature is higher or lower, the yield or selectivity is worse (compare entries 1−3, Table 1). When the reaction was

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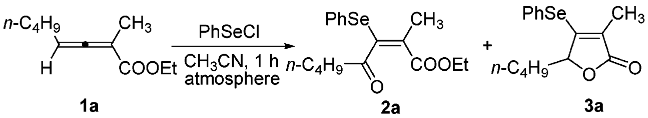
10.1021/jo061680c CCC: $33.50

TABLE 1. Temperature and Concentration Effect on the Reaction of 2,3-Allenoate 1a with PhSeCl[a]



entry	PhSeCl (equiv)	atm	T (°C)	conc of **1a** (mmol/mL)	isolated yields (%) **2a**	**3a**	**2a**/**3a**
1	2.5	air	45	0.2/4	29	5	85:15
2	2.5	air	rt	0.2/4	64	15	81:19
3	2.5	air	−35	0.2/4	61	36	63:37
4	2.5	N_2[b]	rt	0.2/4	31	17	65:35
5[c]	2.5	N_2[b]	rt	0.2/4	54	15	78:22
6[d]	2.5	N_2[b]	rt	0.2/4	62	16	79:21
7	2.5	O_2[b]	rt	0.2/4	42	5	89:11
8	2.0	air	rt	0.2/4	55	17	76:24
9	3.0	air	rt	0.2/4	61	4	94:6
10	3.5	air	rt	0.2/4	62	4	94:6
11	2.5	air	rt	0.8/4	15	19	44:56
12	3.0	air	rt	0.2/6	71[e]	4[e]	95:5
13	3.0	air	rt	0.2/16	72[e]	3[e]	96:4

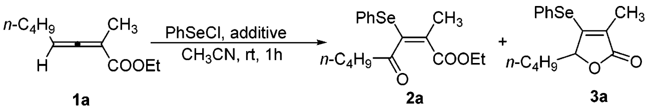
[a] The reaction was carried out using 0.2 mmol of **1a** and PhSeCl in 4 mL of CH_3CN in open air unless otherwise stated. CH_3CN used in the study in Table 1 was distilled once from CaH_2. [b] Air has been carefully removed from the starting reaction mixture. [c] 0.5 equiv of H_2O was added. [d] 1.0 equiv of H_2O was added. [e] Yield determined by ^1H NMR analysis using mesitylene as the internal standard.

conducted in N_2 atmosphere, both the yield and selectivity were poorer (compare entry 4 with entry 2, Table 1). In the presence of water, the reaction under N_2 atmosphere afforded **2a** and **3a** in much higher yields and better selectivities (compare entries 5 and 6 with entry 4, Table 1). The reaction in pure O_2 atmosphere afforded the products in slightly better selectivity, but the yield was low (compare entry 7 with entry 2, Table 1). When 3.0 or 3.5 equiv of PhSeCl were used, the reaction was much more selective and higher yielding (compare entries 2, 8, 9, and 10, Table 1). The concentration for the substrates is also important: with 3.0 equiv of PhSeCl and a concentration of 0.0125 M of **1a**, **2a** was formed in 72% yield while the yield of **3a** was only 3% (compare entries 11−13, Table 1).

However, at such a low concentration the procedure is synthetically unattractive. According to the report by Sharpless et al.,[10] selenate esters may decompose at room temperature to form ketones; thus, we thought that a base may help to facilitate the formation of selenates by its reacting with the in situ generated HCl to improve the selectivity of **2a**/**3a**. Some of representative results are listed in Table 2. It was obvious that the yield and selectivity were improved meaningfully by using different bases with Li_2CO_3 being the best (entries 1−6, Table 2). In fact, with 3.0 equiv of Li_2CO_3, only 2.0 equiv of PhSeCl were required to produce product **2a** in 87% yield and the product **3a** in only 3% yield (compare entry 7 with entry 6, Table 2).

With the standard reaction conditions in hand, the scope of the reaction was explored with some typical results summarized in Table 3. The substituent R^1 may be an alkyl or aryl group and the substituent R^2 may be an alkyl or benzyl group. As determined by ^1H NMR analysis of the crude reaction mixture, the corresponding butenolides were formed in less than 4%. The structure of **2** was further confirmed by the X-ray diffraction study of **2i** (Figure 1, Supprting Information).[11]

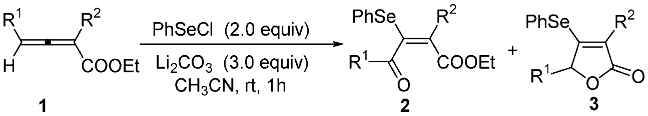
TABLE 2. Optimization of the Reaction Conditions of the Reaction of 1a with PhSeCl[a]



entry	PhSeCl (equiv)	additive (3.0 equiv)	**2a**[b] (%)	**3a**[b] (%)	**2a**/**3a**
1	3.0	Na_2CO_3	80	5	94:6
2	3.0	K_2CO_3	80	11	88:12
3	3.0	Cs_2CO_3	79	5	94:6
4	3.0	LiOH	84	6	93:7
5	3.0	LiOAc	87	4	95:5
6	3.0	Li_2CO_3	87	3	97:3
7	**2.0**	$\mathbf{Li_2CO_3}$	**84**	**3**	**97:3**
8	1.5	Li_2CO_3	67	3	94:6
9[c]	2.0	Li_2CO_3	82	5	94:6

[a] The reaction was carried out using 0.2 mmol of **1a**, PhSeCl, and 3.0 equiv of additive in 6 mL of CH_3CN in open air. [b] Yield determined by ^1H NMR analysis using mesitylene as the internal standard. [c] 2.5 equiv of Li_2CO_3 were added.

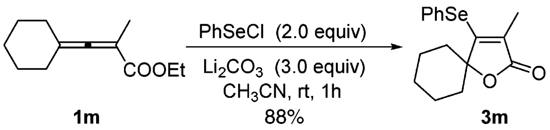
TABLE 3. Reaction of PhSeCl with Different 2,3-Allenoates[a]



entry	R^1	R^2	**2**/**3**[c]	yield[b] of **2** (%)
1	n-C_4H_9	CH_3 (**1a**)	97:3	77 (**2a**)
2[d]	n-C_4H_9	n-C_3H_7 (**1b**)	f	68 (**2b**)
3[d]	n-C_4H_9	Bn (**1c**)	97:3	67 (**2c**)
4	n-C_7H_{15}	CH_3 (**1d**)	f	67 (**2d**)
5	n-C_7H_{15}	n-C_3H_7 (**1e**)	f	63 (**2e**)
6	Ph	CH_3 (**1f**)	97:3	77 (**2f**)
7[e]	Ph	n-C_3H_7 (**1g**)	>99:1	82 (**2g**)
8	Ph	Bn (**1h**)	>99:1	77 (**2h**)
9	p-BrC_6H_4	CH_3 (**1i**)	97:3	63 (**2i**)
10[e]	p-BrC_6H_4	n-C_3H_7 (**1j**)	99:1	85 (**2j**)
11[e]	*a*-naphthyl	CH_3 (**1k**)	98:2	93 (**2k**)
12[e]	*a*-naphthyl	n-C_3H_7 (**1l**)	97:3	89 (**2l**)

[a] The reaction was carried out using 0.2 mmol of 2,3-allenoate, 2.0 equiv of PhSeCl, and 3.0 equiv of Li_2CO_3 in 6 mL of CH_3CN in open air. [b] Isolated yield. [c] Determined by ^1H NMR analysis using mesitylene as the internal standard. [d] Reaction time: 48 h. [e] 3.0 equiv of PhSeCl were used. [f] Due to the overlap of the ^1H NMR signals, it was difficult to determine the ratio of **2**:**3** in this case.

SCHEME 2



As expected, when 2,4,4-trisubstituted 2,3-allenoate **1m** was applied, only butenolide **3m** was isolated in 88% yield indicating the importance of the proton at 4-position of 2,3-allenoates for the formation of 3-phenylseleno-4-oxo-2(E)-enoates **2** (Scheme 2).

The possibility of producing **2a** from butenolide **3a** was excluded on the basis of the following three control experi-

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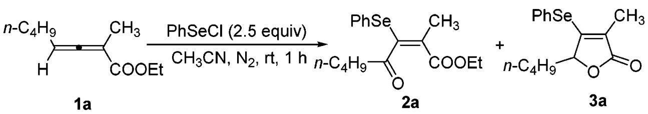
(11) Crystal data for compound **2i**: $C_{19}H_{17}O_{13}BrSe$, $M_w = 452.20$, monoclinic, space group $P2(1)/n$, Mo Kα, final R indices [$I > 2\sigma(I)$], R1 = 0.0548, wR2 = 0.1186, $a = 10.775(13)$ Å, $b = 6.0652(19)$ Å, $c = 28.906(9)$ Å, $\alpha = 90°$, $\beta = 99.145(6)°$, $\gamma = 90°$, $V = 1865.0(10)$ Å^3, $T = 293(2)$ K, $Z = 4$, number of reflections collected/unique: 10370/4046 ($R_{int} = 0.0984$), number of observations: 1454 [$I > 2\sigma(I)$], parameters 219. CCDC 615052.

TABLE 4. Water Effect on the Reaction of 2,3-Allenoate 1a with PhSeCl[a]

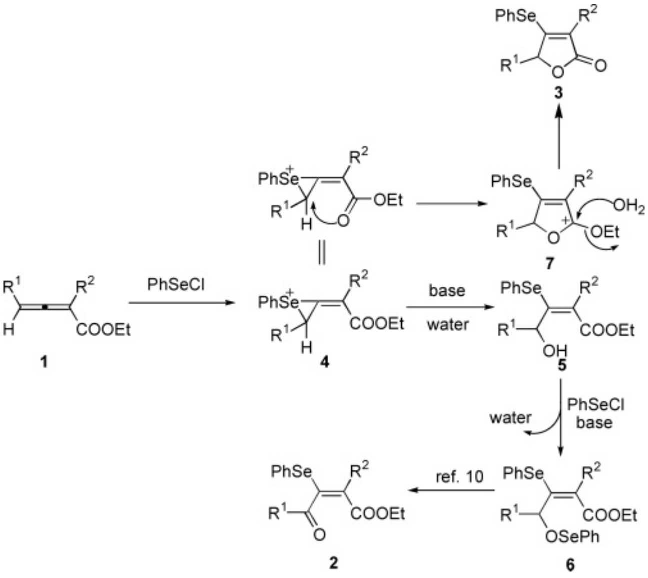


1a **2a** **3a**

entry	H_2O (equiv)	isolated yields (%) 2a	3a
1	0	22	7
2	1.0	61	11
3	1.5	59	20
4	2.5	60	25
5	10	44	44
6	50	2	91
7	111	0	94

[a] The reaction was carried out using 0.2 mmol of **1a** and PhSeCl in 4 mL of CH_3CN (double distilled from CaH_2) under N_2 atmosphere.

SCHEME 3



ments: Compound **3a** is stable in the CH_3CN solution of PhSeCl, even if 1.5 equiv of EtOH were added; there was also no reaction when **3a** was treated in the CH_3CN solution in the presence of 1.0 equiv each of EtOH and HCl.

In order to study the effect of water on the reaction, CH_3CN distilled twice from CaH_2 was used with the addition of different amount of H_2O. The results were summarized in Table 4. From the results, it is quite obvious that the reaction in the presence of a large amount of H_2O afforded lactone **3a**, while with 1.0−2.5 equiv of H_2O the reaction favored the formation of ketoenoate **2a**. The presence of a large amount of H_2O may stabilize the charged intermediates **4**/**7** and facilitate the lactonization process to afford the lactone products (Scheme 3).

Thus, a rationale for this reaction is depicted in Scheme 3. The electrophile PhSeCl reacted with the relatively electron-rich C=C bond in 2,3-allenoates **1** forming intermediates **4**, which may be followed by the attack of H_2O. This process may be faciliated by the presence of Li_2CO_3 to form intermediates **5**.[12] Subsequently, another molecule of PhSeCl reacted with intermediate **5** in the presence of Li_2CO_3 to produce H_2O and intermediate **6**, which may decompose to form the ketone functionality in 3-phenylseleno-4-oxo-2(*E*)-alkenoates **2**.[10] This elimination reaction may be promoted by oxygen.[13] The remaining water in CH_3CN used and the water in open air may responsible for the water effect on this reacton. The stereoselectivity observed may be explained by the favorable *trans* arrangement of the phenylseleno group and the ester group.

In conclusion, we have developed an electrophilic interaction of 2,3-allenoates with PhSeCl affording 3-phenylseleno-4-oxo-2(*E*)-alkenoates in good yields and excellent regio- and stereoselectivity. Although the amount of water in air and commercially available MeCN may be very different, the recation may be easily reproduced by using anhydrous MeCN uner N_2 with the addition of a specified amount of water. As a result of the easy availability of starting materials, the convenient operation, and the usefulness of the products, the reaction may have potential utility in organic synthesis. Further studies in this area including the real role of H_2O in these reactions are being carried out in our laboratory.

Experimental Section

Experimental Preparation of 2-Methyl-4-oxo-3-phenylselanyloct-2(*E*)-enoic Acid Ethyl Ester (2a). Typical Procedure. To a solution of PhSeCl (79.3 mg, 0.41 mmol) in 5 mL of MeCN was added Li_2CO_3 (45.0 mg, 0.61 mmol). Then **1a** (35.6 mg, 0.20 mmol) and 1 mL of MeCN were subsequently added. After being stirred at room temperature for 1 h, the reaction was complete as monitored by TLC and the mixture was filtered through a short column of silica gel to afford the crude product, which was analyzed by 400 MHz ^1H NMR measurement. The crude product was then purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 40:1) to afford **2a** (53.1 mg, 77%). **2a**: liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.0 Hz, 2 H), 7.39−7.27 (m, 3 H), 4.13 (q, J = 7.0 Hz, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.06 (s, 3 H), 1.22 (t, J = 7.0 Hz, 3 H), 1.22−1.13 (m, 2 H), 1.10−0.99 (m, 2 H), 0.73 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 164.7, 150.1, 136.6, 129.33, 129.30, 125.3, 124.2, 61.3, 42.0, 24.6, 21.9, 17.2, 13.9, 13.8; MS (70 eV, EI) m/z 356 (M^+(^{82}Se), 5.72), 355 (M^+(^{80}Se) + 1, 7.13), 354 (M^+(^{80}Se), 28.85), 352 (M^+(^{78}Se), 16.29), 351 (M^+(^{77}Se), 9.26), 350 (M^+(^{76}Se), 7.31), 41 (100); IR ν (cm^{-1}) 2958, 2932, 1704, 1591, 1477, 1465, 1439, 1366, 1270, 1156, 1133, 1022; HRMS calcd for $C_{17}H_{22}O_3{}^{80}SeNa^+$ (M^+ + Na) 377.0638, found 377.0620.

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Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text. X-ray data for compound **2i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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