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Reaction of α-Chloro-α-Phenylselenoesters with Silyl Enol Ethers. Synthesis of α-Phenylseleno-γ-Keto Esters and γ-Butyrolactones.

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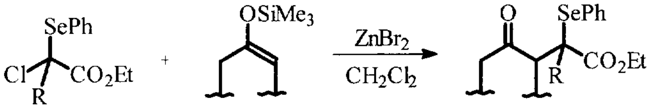
Abstract: *Silyl enol ethers of ketones are alkylated with ethyl α-chloro-α-phenylseleno acetate **1a** or with ethyl α-chloro-α-phenylseleno propionate **1b**, mediated by zinc bromide to give the corresponding α-phenylseleno-γ-keto esters 3 in moderate to good yields.*

Studies concerning to the structure[1] and to synthetic applications of carbocations directly linked to an organoselenium group have been reported over the last few years, involving the reaction of different nucleophiles with selenoacetals,[2] α-halo-α-phenylseleno alkanes,[3] tris-(aryl or alkylseleno)methane,[4] selenoallylic,[5] selenopropargylic[6] and mixed selenium heteroacetals.[7] Recently we described the reaction of ethyl α-halo-α-phenylseleno acetate with arenes[8] and with alkenes mediated by Lewis acid.[9] These reactions exploit the ability of an organoselenium group to stabilize a carbenium ion adjacent to an ester group.

In the course of our studies on selenium-stabilized carbenium ions, we observed that α-chloro-α-phenylselenoesters[10] **1a-b** react with silyl enol ethers **2** mediated by Lewis acids to give α-phenylseleno-γ-keto esters **3** in fair to high yields, in very clean reactions as depicted in Equation 1.



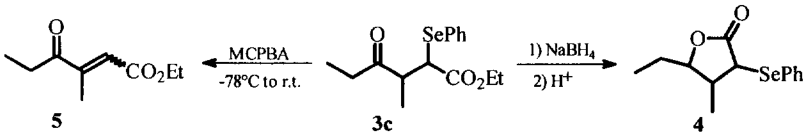
(1)

1a R=H **2** **3**
1b R=CH$_3$

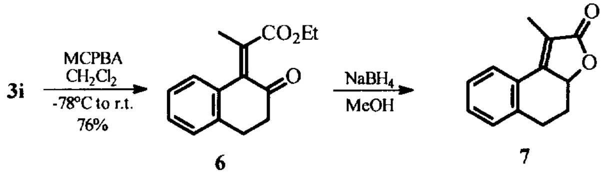
Thus, the treatment[11] of a dichloromethane solution of **1a-b** with 2.0 equivalents of **2a-e** and ZnBr$_2$ as Lewis acid produces the desired adducts **3a-i** (Eq. 1; Table 1). The products are easily purified by silica gel chromatography. Some experimental results are summarized in Table 1, and illustrate the efficiency, applicability and scope of the present method.

From the results described in Table 1, it can be seen that the presence of an additional methyl group in the halide **1b** causes a beneficial effect on the carbocation stabilization. Similar results were obtained previously when the sulfur analogues of **1a** and **1b** were employed in reaction with silyl enol ethers.[12] The yields of the reaction of silyl enol ethers with ethyl α-chloro-α-phenylseleno propionate **1b** in most cases studied are higher than with **1a**, with reaction of silyl enol ether **2b** being one exception (product **3d**; Table 1). The reactions of **1b** were performed at 0°C, but we observed that for the reaction with ethyl α-chloro-α-phenylseleno acetate **1a** better results can be achieved if the reaction is performed at a somewhat higher temperature (room temperature for cyclic ketones or 42 °C for acyclic ketones, oil bath temperature) as shown in Table 1. In the last reactions, a mixture of **1a** and $ZnBr_2$ in dichloromethane was stirred at room temperature or heated at 42 °C for 10 min prior to the addition of the silyl enol ether. All reactions were usually completed within 70 minutes after the addition of compounds **2a-e**. Among the various Lewis acid tried, $ZnBr_2$ gave the best results, although $ZnCl_2$ also reacted efficiently. When $AlCl_3$, $TiCl_4$ and $SnCl_4$ were used, rapid decomposition of the silyl enol ether was observed by TLC and no products were detected. It is interesting to note that the use of dichloromethane dried from P_2O_5 as a solvent gives better results than the use of one distilled from CaH_2.[13]

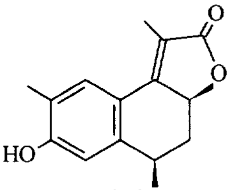
To illustrate some possible synthetic uses of the compounds obtained, the adduct derived from pentan-3-one **3c** was subjected to some transformations. Treatment of **3c** with $NaBH_4$ followed by acid treatment (Equation 2) results in the formation of the corresponding lactone **4** in 73% yield as a mixture of four diastereoisomers (27 : 17 : 38 : 19) determined by GC. Adduct **3c** was also subjected to oxidation with MCPBA[14] to produce **5** in 82% yield, as two stereoisomers in a 4.1 : 1 ratio, as determined by ^1H NMR (Equation 2). The ester **3i**, derived from the silyl enol ether **2e**, was subjected to elimination with MCPBA to give **6** in 76% yield, which was subsequently reduced with $NaBH_4$ in methanol to give directly 7 in one step (Equation 3). The adduct **7** was prepared as a model compound to the synthesis of the natural product (±)-Heritol[15] **8**. Studies are underway to apply the present methodology to the synthesis of **8** and the results will be described in due course.



(2)



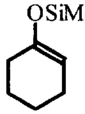
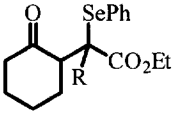
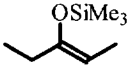
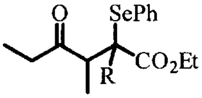
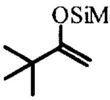
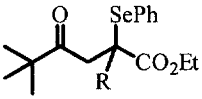
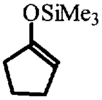
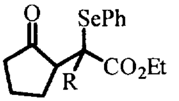
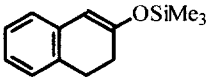
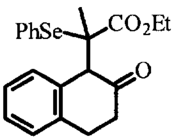
(3)



(+)-Heritol **8**

The kind of products prepared, combining several functionalities, should find broad application in organic synthesis. Studies on microbiological reductions of keto groups in type **3** compounds using Baker Yeast[16] are underway in our laboratories. In this way, asymmetric synthesis of γ-substituted-α,β-unsaturated butenolides could be possible using the reactions described in this communication.

Table 1. α-Phenylseleno-γ-Keto Esters obtained.

	Silyl Enol Ether	Product[a]		Reaction temp.	Yield (%)[b]
2a			3a, R=H	r.t.[c]	60
			3b, R=Me	0°C	73
2b			3c, R=H	r.t.	66
			3c, R=H	42°C	86
			3d, R=Me	0	80
2c			3e, R=H	r.t.	47
			3e, R=H	42°C	56
			3f, R=Me	0°C	71
2d			3g, R=H	r.t.[c]	42
			3h, R=Me	0°C	81
2e			3i	0°C	58

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[a] Compounds **3a-d** and **3g-i** were formed as a mixture of two diastereoisomers (GC and ^{1}H NMR). [b] Isolated yields. [c] Lower yields were obseved at 42°C.

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10. a) Compound **1a** was obtained as previously described: Dabdoub, M. J.; Guerrero Jr., P. G.; Silveira, C. C. *J. Organometal. Chem.* **1993,** *460*, 31. b) **1b** was obtained as previously described by: Banem, B.; Ikota, N. *J. Org. Chem.*, **1978,** *43*, 1607.
11. **Typical procedure for the synthesis of compounds 3a-i**. $ZnBr_2$ (0.17 g, 0.76 mmol) was added to a stirred solution of **1a** or **1b** (1 mmol) in CH_2Cl_2 (3 mL) under nitrogen. The mixture was stirred for 10 min. at the temperature indicate in Table 1. The silyl enol ether (2 mmol) was added, the reaction mixture was stirred for an additional 70 min, water was added and the product extracted with EtOAc (2 x 50 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under vacuo to give a brown oil. The product was purified by flash column chromatography on SiO_2, using a mixture of hexane/EtOAc (9/1) as eluent to yield γ-keto esters **3a-i** (Table 1). For compound **3f**: ^1H NMR 1.00(s, 9H), 1.02(t, J=7.0, 3H), 1.47(s, 3H), 2.78 and 3.21(2d, AB, J=17.9, 2H), 3.94(q, J=7.0, 2H), 7.06-7.55(m, 5H) ^{13}C NMR : 12.7; 21.9; 25.1; 42.8; 44.8; 59.5; 125.8; 127.6; 128.35; 136.95; 172.0; 211.1. **I.R.** (C=O)ν (cm^{-1}) 1712. *Anal.* calcd. for $C_{17}H_{24}SeO_3$ C, 57.29; H, 6.79. Found C, 57.14 ; H, 6.79%; **M. S.** *m/z* : 353 (M^+-2, 90%); 310(100%); 200(12%).
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14. Oxidation of **3c** with MCPBA. To a stirred solution of γ-keto ester (1.0 mmol) in CH_2Cl_2 (20 mL) under nitrogen at -78°C, MCPBA (0.414g, 1.2 mmol, 50 %) was added. After the end of addition, the reaction mixture was warmed slowly to room temperature and stirred for one additional hour at room temperature. The reaction mixture was quenched with a saturated aq. solution of $NaHCO_3$. The organic phase was washed with a saturated solution of NH_4Cl, then dried over $MgSO_4$ and the solvent removed under vacuo to give a yellow oil that was purified by flash chromatography on SiO_2, using a mixture of hexane/EtOAc as eluent (8.5/1.5) to yield the α,β-unsatured carbonyl compound **5** in 82% yield.
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