Electrochemical Functionalization of Chalcogeno Compounds. Regioselective Anodic Acetoxylation of Selenides Bearing Electron-Withdrawing Groups[1]

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Although α-functionalization of amines and arenes is well-established, such functionalization of chalcogeno compounds has been limited and undeveloped.[2,3] For example, it is known that anodic acetoxylation of sulfides takes place only when the concentration of both a substrate and a supporting electrolyte, acetate ions, is extremely high.[4] From a synthetic viewpoint, this is not so practical, particularly on a large scale.

Recently, we have found that anodic acetoxylation of sulfides was remarkably promoted by strong electron-withdrawing perfluoroalkyl groups even at low concentrations.[5-7] This finding prompted us to attempt anodic acetoxylation of other chalcogeno compounds, selenides. So far, no report has been made on anodic substitution of organo selenium compounds. Moreover, although selenoetherification and selenolactonization using anodic oxidation of diselenides are well-known,[8] very few studies on anodic oxidation of selenides have been performed.[9]

In this paper, we wish to report the first example of successful anodic α-substitution of selenides bearing various electron-withdrawing groups (EWG's) 1.

Results and Discussion

Oxidation Potentials of Selenides. In order to investigate the effect of electron-withdrawing substituents on the oxidation potentials of selenides, the oxidation potentials of selenides **1c–1h** together with simple selenides **1a** and **1b** were measured at a platinum anode in acetonitrile using cyclic voltammetry (CV). These selenides exhibited multiple irreversible anodic waves, and the first peak potentials are summarized in Table I.

Selenides bearing EWG were found to be oxidized at more positive potentials than simple alkyl phenyl selenides. A large anodic shift was observed in the case of strong EWG's such as cyano (CN) and perfluoroalkyl (C_nF_{2n+1}) groups. It should be noted that selenides **1c** and **1g** show almost equal oxidation potentials although the CN group has a stronger electron-withdrawing effect than CF_3 (σ^* of CH_2CN = 1.30; σ^* of CH_2CF_3 = 0.92).[10,11]

Anodic Acetoxylation of Selenides. The anodic acetoxylation of selenides was carried out at platinum electrodes in AcONa/AcOH using an undivided cell. After passing constant current of 4 F/mol, usual workup was performed. The results are summarized in Table II.

α-Acetoxylation of selenides bearing EWG's was successfully performed. On the contrary, simple selenides devoid of EWG's **1a** and **1b** gave only a trace amount of the desired products, and a relatively large amount of diphenyl diselenide **3** was detected in the electrolysis of **1b**. Perfluoroalkyl groups promoted the anodic acetoxylation most efficiently. This is noticeable because nucleophilic substitution at the position α to the perfluoroalkyl groups is generally quite difficult to achieve.[12] In contrast, the β-trifluoromethyl group facilitated the acetoxylation much less effectively, and a large amount of diselenide **3** was formed. Each selenide bearing less strong electron-withdrawing ester group **1h** gave a desired product is reasonable yield. In our previous paper, we have shown that stronger EWG promotes anodic substitution of sulfides with oxygen nucleophiles more efficiently since the stronger EWG facilitates deprotonation of cation radical

Table I. Oxidation Potentials (Peak Potentials, E_p^{ox}) of Selenides[a]

[$PhSeCH_2$–EWG]

selenide no.	EWG	E_p^{ox} (V) vs SCE
1a	H	1.32
1b	CH_3	1.37
1c	CF_3	1.70
1d	C_2F_5	1.71
1e	C_3F_7	1.72
1f	CH_2CF_3	1.50
1g	CN	1.70
1h	COOEt	1.50

[a] 5 mM of selenide in 0.1 M n-Bu_4NBF_4/CH_3CN. Sweep rate: 100 mV/s.

Table II. Anodic Acetoxylation of Selenides[a]

$$\underset{\mathbf{1}}{PhSeCH_2\text{–}EWG} \xrightarrow[AcONa/AcOH]{-2e,\,-H^+} \underset{\mathbf{2}}{PhSeCH(OAc)\text{–}EWG} + \underset{\mathbf{3}}{PhSeSePh}$$

selenide no.	EWG	current density (mA/cm²)	conversn (%)	products (yield, %)[b] 2	3
1a	H	2.5	41	trace	0
1b	CH_3	2.5	32	trace	17
1c	CF_3	4.5	96	67	6
1d	C_2F_5	4.5	97	61	1
1e	C_3F_7	4.5	99	69	0
1f	CH_2CF_3	4.5	64	31	25
1g	CN	6.8	94	50	10
1h	COOEt	4.5	100[c]	45	7

[a] Electricity passed: 4 F/mol. [b] Based on consumed starting material 1. [c] Electricity passed: 8 F/mol.

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intermediates formed from one-electron oxidation of the sulfides more effectively.[7] In fact, we have found that anodic acetoxylation of cyanomethyl phenyl sulfide took place highly efficiently.[13] Therefore, it was expected that selenide having a CN group **1g** should provide the corresponding acetoxylated product **2g** in high yield; however, the yield was moderate and, in this case, a considerable amount of 3 was formed. It was found that **2g** easily decomposes at room temperature to give **3**. Therefore, **3** seems to be partly formed during separation of **2g** by chromatography.

Acetoxylated products are monoselenoacetals bearing EWG's, particularly, α-perfluoroalkyl monoselenoacetals **2c–2e** seem to be highly useful building blocks similar to those of sulfur analogues reported before.[6] So far, only limited methods have been developed for the preparation of selenoacetals, which require rather complicated procedures or special reagents.[14] In this point, this electrochemical method has advantages since monoselenoacetals can be prepared in one step under mild conditions.[15]

Experimental Section

^{1}H NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ at 60 MHz on JEOL JNM-PMX 60 and at 470 MHz on Varian VXR-500 spectrometers, respectively. The chemical shifts for ^{1}H and ^{19}F NMR are given in δ ppm downfield from Me_4Si and $CFCl_3$ as internal standard, respectively.

The purity of all title compounds was judged to be >95% by ^{1}H NMR spectral determinations.

Preparation of Selenides. Ordinary selenides were prepared according to the procedure described in the literature.[16] Phenylselenide anion is generated by the reaction of diphenyldiselenide with sodium borohydride in ethanol, and then reaction with the corresponding alkyl halide provides the desired alkyl phenyl selenide. In this way CH_3J, C_2H_5J, $BrCH_2CH_2CF_3$, $BrCH_2CN$, and $ClCH_2COOEt$ were used to provide $PhSeCH_3$ (**1a**)[17] (41%), $PhSeCH_2CH_3$ (**1b**)[18] (76%), $PhSeCH_2CH_2CF_3$ (**1f**) (95%), $PhSeCH_2CN$ (**1g**)[19] (95%), and $PhSeCH_2COOEt$ (**1h**)[20] (87%), respectively.

Since the known procedure[21] of preparation of $PhSeCH_2CF_3$ (**1c**) is too complicated, in this work, 1,1-dihydroperfluoroalkyl phenyl selenides **1c–1e** were obtained by the reaction of PhSeNa with the corresponding 1,1-dihydroperfluoroalkyl tosylate in a manner similar to the preparation method of 1,1-dihydroperfluoroalkyl sulfides.[6,7] The selenide **1c** was prepared as follows. After generation of PhSeNa from 1.56 g (5 mmol) of PhSeSePh and 0.42 g (11 mmol) of $NaBH_4$ in 50 mL of ethanol, the ethanol was removed under reduced pressure, and then 50 mL of DMF was added. The resulting solution was stirred at 60 °C in the dark. After 7 h, the reaction was quenched by the addition of 0.1 M hydrochloric acid and extracted repeatedly with ether, and then the ether extracts were washed with $NaHCO_3$, water, and brine and then dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was distilled using a Kugelrohr apparatus at 90 °C (6 mmHg) to provide 1.50 g (63%) of pure **1c** as an oil. In the case of $PhSeCH_2C_2F_5$ (**1d**) and $PhSeCH_2C_3F_7$ (**1e**), the reaction was carried out in THF containing 10% of HMPA. Separation using silica gel chromatography (hexane) provided **1d** (72%) and **1e** (70%).

1,1,1,2,2-Pentafluoro-3-(phenylseleno)propane (1d): ^{1}H NMR δ 3.33 (t, 2 H, J = 18 Hz, CH_2), 7.07–7.78 (m, 5 H, Ph); ^{19}F NMR δ −115.198 (t, 2 F, J = 17.93 Hz, CF_2CF_3), −85.649 (s, 3 F, CF_3); IR (neat) 3080, 2860, 1580, 1480, 1460, 1420, 1350, 1200, 1060, 1010, 740, 690, 660, 520, 470 cm^{-1}; MS m/e 290 (M^+), 157 ($PhSe^+$); calcd for $C_9H_7F_5{}^{80}Se$ m/e 289.9632, found m/e 289.9628. Anal. Calcd: C, 37.39; H, 2.44. Found: C, 37.50; H, 2.64.

1,1,1,2,2,3,3-Heptafluoro-4-(phenylseleno)butane (1e): ^{1}H NMR δ 3.37 (t, 2 H, J = 18.5 Hz, CH_2), 7.08–7.74 (m, 5 H, Ph); IR (neat) 3080, 2980, 1585, 1485, 1445, 1420, 1355, 1260, 1110, 1025, 1000, 960, 930, 730, 690, 670, 625, 530, 470 cm^{-1}; MS m/e 340 (M^+), 157 ($PhSe^+$); calcd for $C_{10}H_7F_7{}^{80}Se$ m/e 339.9600, found m/e 339.9536.

1,1,1-Trifluoro-3-(phenylseleno)propane (1f): ^{1}H NMR δ 2.07–2.64 (m, 2 H, CH_2CF_3), 2.64–3.16 (m, 2 H, $CH_2CH_2CF_3$) 7.05–7.65 (m, 5 H, Ph); ^{19}F NMR δ −67.939 (t, 3 F, J = 10.30 Hz, CF_3); IR (neat) 3080, 2950, 1580, 1480, 1445, 1370, 1260, 1210, 1130, 1080, 1020, 1000, 930, 840, 730, 690, 600, 470 cm^{-1}; MS m/e 254 (M^+), 171 ($M^+ - CH_2CF_3$), 157 ($PhSe^+$); calcd for $C_9H_9F_3{}^{80}Se$ m/e 253.9820, found m/e 253.9768. Anal. Calcd: C, 42.72; H, 3.58. Found: C, 42.98; H, 3.85.

Ethyl 1-(phenylseleno)acetate (1h):[20] ^{1}H NMR, δ 1.8 (t, 3 H, J = 7 Hz, CH_2CH_3), 3.45 (s, 2 H, CH_2CH_3), 4.08 (q, 2 H, J = 7 Hz, $SeCH_2$), 7.1–7.7 (m, 5 H, Ph).

Electrolysis. Electrolysis was carried out at a constant current using platinum plates (1.2 × 3.7 cm) as an anode and a cathode in an undivided cell equipped with a magnetic stirrer. Electrolysis of selenides **1** (2 mmol) was carried out in 0.2 M AcONa/AcOH (30 mL) at 50 °C. Electrolytic conditions in each electrolysis are shown in Table II. After passing 4 F/mol of electricity the electrolytic solution was mixed with 40 mL of water and extracted three times with 20-mL portions of ether. The extracts were combined and washed with $NaHCO_3$, water, and brine and then dried ($MgSO_4$). After evaporation of solvent under reduced pressure, the residue was chromatographed on silica gel (preparative thin-layer chromatography (TLC) using hexane or hexane–AcOEt/20:1–9:1) to provide pure **2**.

2-Acetoxy-1,1,1-trifluoro-2-(phenylseleno)ethane (2c). From 0.478 g (2 mmol) of **1c** was obtained 380 mg (64%; 67% based on consumed **1c**) of pure **2c** after TLC separation (hexane–AcOEt (19:1)): ^{1}H NMR δ 2.12 (s, 3 H, CH_3), 6.38 (q, 1 H, J = 7.5 Hz, $CHCF_3$), 7.23–7.92 (m, 5 H, Ph); IR 3070, 2980, 1780 (CO), 1580, 1480, 1440, 1370, 1270, 1180, 1110, 1040, 1000, 910, 855, 740, 680, 630, 560, 480, 460 cm^{-1}; MS m/e 298 (M^+), 200 ($PhSeCOCH_3^+$), 158 ($PhSeH^+$); calcd for $C_{10}H_9F_3O_2{}^{80}Se$ m/e 297.9719, found m/e 297.9723. Anal. Calcd: C, 40.42; H, 3.05. Found: C, 40.23; H, 3.30.

3-Acetoxy-1,1,1,2,2-pentafluoro-3-(phenylseleno)propane (2d): ^{1}H NMR δ 2.06 (s, 3 H, CH_3), 6.47 (dd, 1 H, J = 20, 6 Hz, CHC_2F_5), 7.15–7.80 (m, 5 H, Ph); IR 3080, 3000, 1780 (CO), 1580, 1480, 1445, 1380, 1345, 1200, 1140, 1020, 900, 805, 740, 700, 640, 580, 505, 470 cm^{-1}; MS m/e 348 (M^+), 157 ($PhSe^+$), 78 (PhH^+); calcd for $C_{11}H_9F_5O_2{}^{80}Se$ m/e 347.9688, found m/e 347.9695. Anal. Calcd: C, 38.06; H, 2.61. Found: C, 38.35; H, 2.88.

4-Acetoxy-1,1,1,2,2,3,3-heptafluoro-4-(phenylseleno)butane (2e): ^{1}H NMR δ 2.05 (s, 3 H, CH_3), 6.49 (dd, 1 H, J = 20, 5 Hz, CHC_3F_7), 7.09–7.79 (m, 5 H, Ph); IR 3070, 2990, 1780, (CO), 1580, 1480, 1445, 1200, 890, 740, 690, 655, 525, 465 cm^{-1}; MS m/e 398 (M^+), 200 ($PhSeCOCH_3^+$), 158 ($PhSeH^+$), 78 (PhH^+); calcd for $C_{12}H_9F_7O_2{}^{80}Se$ m/e 397.9655, found m/e 397.9612. Anal. Calcd: C, 36.29; H, 2.28. Found: C, 36.43; H, 2.18.

3-Acetoxy-1,1,1-trifluoro-3-(phenylseleno)propane (2f): ^{1}H NMR δ 2.05 (s, 3 H, CH_3), 2.60 (dq, 2 H, J = 10, 6 Hz, $CHCH_2CF_3$), 6.43 (t, 1 H, J = 7 Hz, $CHCH_2CF_3$), 7.16–7.74 (m, 5 H, Ph); IR 3080, 2980, 1770 (CO), 1580, 1480, 1440, 1380, 1330, 1270, 1220, 1140, 1080, 1020, 970, 940, 830, 745, 690, 620, 460 cm^{-1}; MS m/e 312 (M^+), 200 ($PhSeCOCH_3^+$), 157 ($PhSe^+$); calcd for $C_{11}H_{11}F_3O_2{}^{80}Se$ m/e 311.9875, found m/e 311.9868.

Acetoxy(phenylseleno)acetonitrile (2g): ^{1}H NMR δ 2.13 (s, 3 H, CH_3), 6.55 (s, 1 H, CHCN), 7.15–7.83 (m, 5 H, Ph); IR

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3070, 2950, 2250 (CN), 1780 (CO), 1440, 1375, 1210, 1020, 740, 690 cm^{-1}; MS m/e 255 (M^+), 200 ($PhSeCOCH_3^+$), 158 ($PhSeH^+$), 43 ($COCH_3^+$); calcd for $C_{10}H_9NO_2{}^{80}Se$ m/e 254.9798, found m/e 254.9856.

Ethyl 1-acetoxy-1-(phenylseleno)acetate (2h): ^1H NMR δ 1.16 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.13 (s, 3 H, $COCH_3$), 4.05 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.32 (s, 1 H, CH), 7.13–7.73 (m, 5 H, Ph); IR 3070, 3000, 1760 (CO), 1580, 1480, 910, 860, 690, 650, 610, 500, 470 cm^{-1}; MS m/e 302 (M^+), 200 ($PhSeCOCH_3^+$), 158 ($PhSeH^+$), 78 (PhH^+); calcd for $C_{12}H_{14}O_4{}^{80}Se$ m/e 302.0028, found m/e 302.0025. Anal. Calcd: C, 47.85; H, 4.69. Found: C, 47.64; H, 4.81.

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Supplementary Material Available: ^1H NMR spectra of new compounds (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of (2*RS*,4′*R*,8′*R*)-α-Tocopherol and Related Compounds via a 2-Chlorochroman

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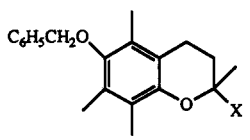
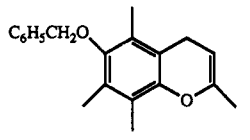
We describe a new synthetic route to 2,2-disubstituted chromans involving coupling of the novel 2-chlorochroman **4** with nucleophiles.[1] This approach has been employed in a synthesis of (2*RS*,4′*R*,8′*R*)-α-tocopherol[2] as the corresponding benzyl ether **1** and was stimulated by a desire to find additional applications for intermediates such as **2**[3] and **3**.[3] The latter compounds are readily available via the cyclocondensation of trimethyl hydroquinone with methyl vinyl ketone, a key reaction discovered several years ago in our laboratories,[4] and are thus attractive starting points for the development of new routes to the tocopherol class of antioxidants. In this context, we envisioned chloride **4** as being easily obtained from hemiketal **3** and serving as an electrophilic chroman component in various coupling processes.

Highly reactive cyclic α-halo ethers have recently found synthetic utility outside of the carbohydrate field. In particular, Bates (Bihovsky) and co-workers[5] have described reactions of 2-chlorotetrahydropyrans and related intermediates with various nucleophiles. A search of the literature revealed that 2-halochromans, on the other hand, are a relatively rare species.[6] We were particularly concerned about the properties of compounds such as **4** in which the halogen is attached to a tertiary center. Not only did we expect such substances to be unstable, we were also aware that their reactivity pattern in nucleophilic coupling processes would probably lead to substantial amounts of elimination products (chromenes). While these caveats certainly turned out to be justified, we have, nonetheless, uncovered some synthetically useful transformations of the chlorochroman **4**.

Treatment of the hemiketal **3** with HCl in ether at 0 °C[5a] gave **4** in 93% yield as a solid which could be stored indefinitely at 0 °C without deterioration but which rapidly decomposed on exposure to moisture or silica gel. Substitution reactions of **4** with various nucleophiles, not unexpectedly, gave mixtures of the desired coupling products and the elimination product chromene **10**.[7] Exposure of **4** to dimethyl sodiomalonate in THF[5a] gave diester **7** in 23% yield. This product is a precursor to chroman-2-acetic acids (e.g. **8**) of established utility in α-tocopherol synthesis.[3a,4,8] All attempts to obtain nitrile **9**, a potential precursor to antioxidant chroman-2-carboxylic acids,[3b,9] by treatment of **4** with alkali metal cyanides proved fruitless, the chromene **10** again being the major identifiable product. Even phase-transfer conditions afforded only trace quantities of the desired nitrile.



1; X= (4*R*,8*R*)-4,8,12-trimethyltridecyl
2; X= OCH_3
3; X= OH
4; X= Cl
5; X= C_2H_5
6; X= $CH_2CH{=}CH_2$
7; X= $CH(CO_2CH_3)_2$
8; X= CH_2CO_2H
9; X= CN



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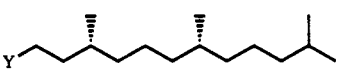
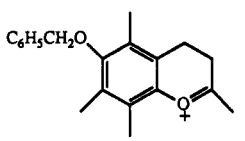


11; Y= OH
12; Y= CH_2OH
13; Y= CH_2Br
14; Y= CH_2MgBr



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The reactions of **4** with Grignard reagents (ethylmagnesium bromide, allylmagnesium chloride, C_{16}-side

(1) This work is the subject of U.S. Patents No. 4,752,646 (June 21, 1988), 4,806,661 (Feb 21, 1989), and 4,824,971 (April 25, 1989), Hoffmann-La Roche, Inc.

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