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# Reactions of 2,4,6-Tri-*t*-butylphenyllithium with Deuterated Formate, Thioformate, and Selenoformate

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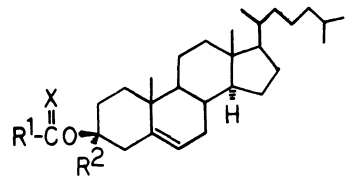
*O*-Cholesteryl chalcogenoformates-*d*, DC(=X)(OR) (**2**: X=O; **3**: X=S; **4**: X=Se; R=3*β*-cholesteryl), were synthesized and allowed to react with 2,4,6-tri-*t*-butylphenyllithium. 1,3,5-Tri-*t*-butylbenzene was a main product in each reaction. The other products were 2,4,6-tri-*t*-butylbenzaldehyde-*d* (**9**) for **2**, 2,4,6-tri-*t*-butylthiobenzaldehyde-*d* for **3**, and **9**, 6,8-di-*t*-butyl-1-deuterio-3,4-dihydro-4,4-dimethyl-1*H*-2-benzoselenin, bis(2,4,6-tri-*t*-butyl-*α*-deuteriobenzyl) diselenide, and bis(2,4,6-tri-*t*-butyl-*α*-deuteriobenzyl) triselenide for **4**. The mechanisms for these reactions have been discussed.

We have previously reported[1] that 2,4,6-tri-*t*-butylphenyllithium (**1**) reacts with selenoformates at three different sites (i.e. the selenoformyl hydrogen, the selenoformyl carbon, and the selenium atoms). We became interested in the hydrogen abstraction from the selenoformyl group and studied similar abstraction reactions of a series of chalcogen analogs **2**—**4** having a deuterated formyl group in order to elucidate the effect of these heteroatoms on the reactivity and the mechanism of these reactions.



**2** X=O; $R^1$=D, $R^2$=H
**3** X=S; $R^1$=D, $R^2$=H
**4** X=Se; $R^1$=D, $R^2$=H
**5** X=Se; $R^1$=H, $R^2$=H
**6** X=Se; $R^1$=H, $R^2$=D

**Syntheses of Formate 2 and Thioformate 3.** Deuterated compounds **2** and **3** were synthesized by the reaction of iminium salt **7**,[2] prepared from *N*,*N*-dimethylformamide-$d_7$, with cholesterol followed by treatment with water and hydrogen sulfide, respectively.

$$\mathrm{D\text{-}\overset{Cl}{\overset{|}{C}}{=}\overset{+}{N}(CD_3)_2} + \mathrm{ROH} \longrightarrow \mathrm{D\text{-}\overset{OR}{\overset{|}{C}}{=}\overset{+}{N}(CD_3)_2}$$

**7**

$$\longrightarrow \mathrm{D\text{-}\overset{OR}{\overset{|}{C}}{=}X} \quad (\mathrm{H_2X})$$

**2**: X=O 96%
**3**: X=S 33%
R=3*β*-cholesteryl

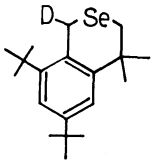
**Reactions with 2,4,6,-Tri-*t*-butylphenyllithium (1).** The esters **2**—**4** were allowed to react with **1**, prepared from 1-bromo-2,4,6-tri-*t*-butylbenzene with 2 equiv of *t*-butyllithium, at −78 °C in tetrahydrofuran (THF). The reaction mixtures were allowed to warm to room temperature in the reactions of **2** and **3** or to 60 °C in the reaction with **4**. The results are listed in Table 1.#

# Throughout this paper, Ar denotes 2,4,6-tri-*t*-butylphenyl.

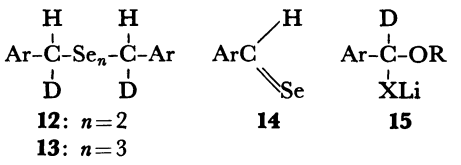
The formate **2** afforded mostly 1,3,5-tri-*t*-butylbenzene (**8**) along with a small amount of deuterated 2,4,6-tri-*t*-butylbenzaldehyde (**9**). The thioformate **3** gave rise to similar products (**8** and **10**), but the yield of **8** was decreased when compared with the reaction of **2**. The reaction of **4** resulted in an even smaller amount of **8**; **9** and other four products **11**—**13**, and $(ArSe)_2$[1] being also formed. It has been reported that **11** and **9** are formed by cyclization of 2,4,6-tri-*t*-butylselenobenzaldehyde-*d* (**14**) and hydrolysis of the initial adduct **15** (X=Se), respectively.[1] The mechanism for the formation of **12** and **13** will be discussed later.

$$\mathrm{ArLi} + \mathrm{D\text{-}\overset{X}{\overset{\|}{C}}\text{-}OR} \longrightarrow \mathrm{ArD\ (or\ ArH)} + \mathrm{ArC\text{-}\overset{X}{\overset{\|}{C}}\text{-}D} + \mathrm{Others}$$

**8** **9**: X=O **10**: X=S



**11**

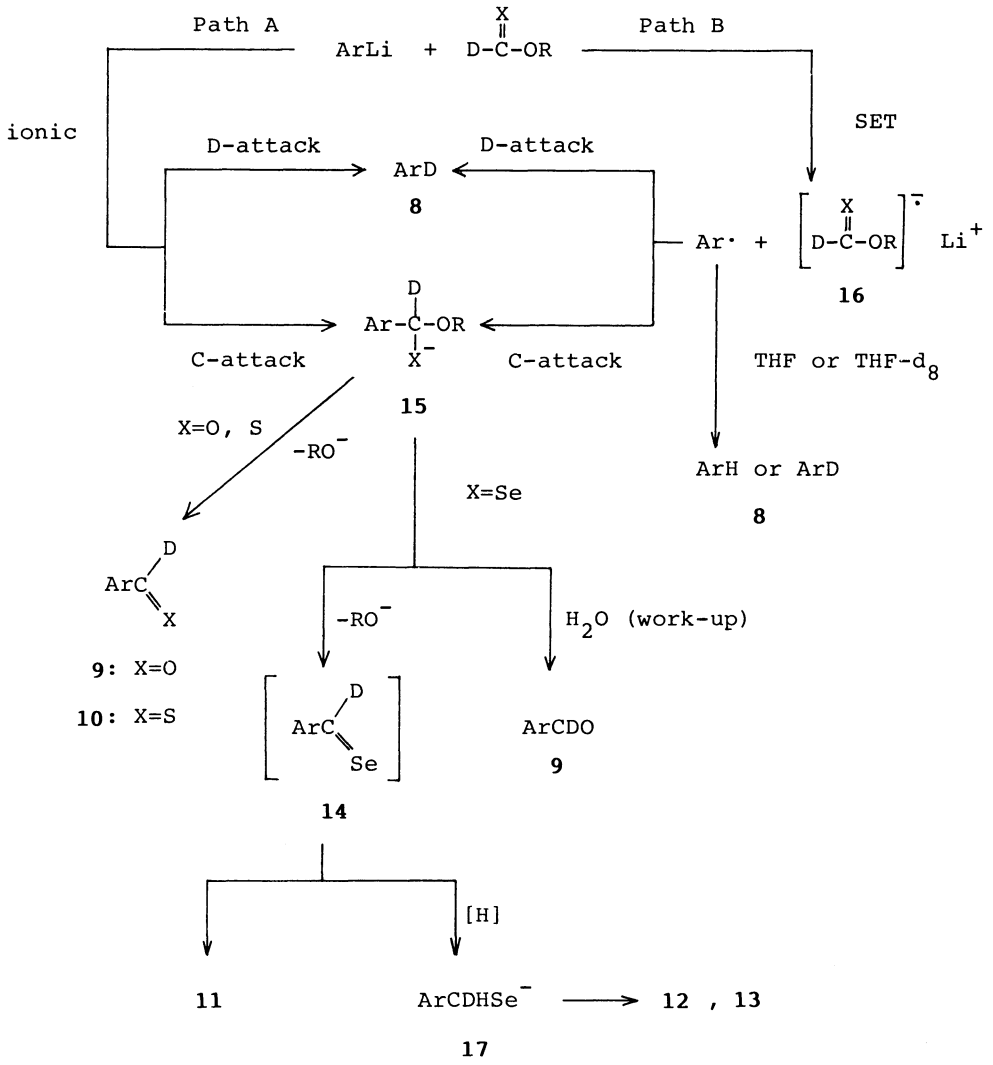


**12**: *n*=2
**13**: *n*=3
**14** **15**

**Reaction Mechanism.** There are two conceivable mechanisms for the reaction of ArLi with the formates **2**—**4** (Scheme 1); one is an ionic mechanism (Path A) and the other is a homolytic one involving single electron transfer (SET) from ArLi to the formates (Path B)(Scheme 1).[3] The following experiments using THF-$d_8$ as a solvent clearly show that Path B involving Ar· is operative in these reactions. Thus, the quenching of a THF-$d_8$ solution of ArLi after 35 min of the preparation gave ArH (88% yield) with no deuterium (by MS), while a similar experiment with the selenoformate **5** (having a HC(=Se) group) added soon after the preparation of ArLi gave ArH (37%) containing 2.6±0.4% deuterium (by MS). The formation of ArD in the latter reaction can be explained only in terms of the abstraction of deuterium from THF-$d_8$ by 2,4,6-tri-*t*-butylphenyl radical Ar· which is formed by SET from ArLi to **5**, since the former reaction shows that ArLi itself is stable under the reaction conditions and can not react

with THF-$d_8$ to give ArD. Although the possibility that Path A and Path B are both operative in these reactions can not be excluded, we consider that the formation of all the reaction products can be accounted for in terms of Path B as shown in Scheme 1.

As can be seen from Table 1, the yield and deuterium content of 1,3,5-tri-*t*-butylbenzene show an interesting and systematic change depending on the heteroatoms in the formates **2**—**4**. The results suggest that the relative rate of the reaction of Ar· with anion radical **16** is in the order of O>S>Se for D-attack and O<S<Se for C-attack. This is probably related to the spin density on the duterium and the carbon of the anion radical **16**. ArH is most probably formed from the reactions of Ar· and unreacted ArLi with THF. Actually ArLi was found to react with THF to give ArH at room temperature.




Scheme 1.

Table 1. Products and Yields of the Reactions of **1** with Esters **2**—**4**

| Ester | Product Yield/% | | | |
|---|---|---|---|---|
| | ArH + ArD(%d) (**8**) | ArCDO (**9**) | ArCDS (**10**) | Others |
| **2** | 86 (41.0±0.2) | 3 | | |
| **3** | 51 (21.5±0.9) | | 37 | |
| **4** | 35 ( 5.8±0.1) | 16 | | **11**(2), **12**(8) **13**(14), $(ArSe)_2$(trace) |

Selenides **12** and **13** are considered to be formed during work-up procedure by the oxidative coupling of selenide ion **17** with another molecule of **17** and $ArCHDSe_2^-$ which is formed from **17** and selenium, respectively. Since **17** is a reduced form of **14**, some attempts to clarify the formation mechanism of **17** were carried out. Since it has been reported that an alkoxide ion derived from an alcohol having α-hydrogen atom can reduce thioketones,[4] one possible reducing agent of selenoaldehyde **14** is a cholesteryl-oxide anion formed from **15**. To check this possibility, selenoformate **6** was synthesized from the corresponding 3α-deuteriocholesterol and was allowed to react with ArLi under the conditions identical with those for **4**. The products were ArH (38%), ArCHO (2%), 6,8-di-*t*-butyl-3,4-dihydro-4,4-dimethyl-1*H*-2-benzoselenin (9%), and $ArCH_2Se_nCH_2$-Ar (**18**, $n$=2, 9%; $n$=3, 9%). Since **18** thus formed contained no deuterium, the above possibility was excluded. The mechanism for the formation of **12** and **13** is not clear at present.

The formation of **8** in a high yield in the reactions with the formate **2** suggests a possibility of the existence of anion $^-C(=O)(OR)$ **19** in solution. The anion **19** is an interesting species since it is an umpolung species of chloroformate ClC(=O)(OR) and enables the synthetically useful process, HC(=O)-(OR)→R′C(=O)(OR), if it is quenched with electrophiles such as aldehydes and alkyl halides.[5] To check this possibility, the reactions of ArLi with some formates HC(=O)(OR) (**20**, R=cholesteryl, *i*-Pr, *t*-Bu) were carried out at low temperatures (−78—−98 °C) and quenched with benzaldehyde, benzophenone, and benzyl chloride. The products, however, were **8** and ArCHO, no trapping of **19** being observed. This is probably due to high instability of **19**, which decomposes into carbon monoxide and an alkoxide ion.[6]

Table 2. Attempted Trapping Experiments of Anion **19**

| R of **20**/equiv | Temp/°C | Quencher/equiv |
|---|---|---|
| *i*-Pr (5) | −78 | $PhCH_2Cl$ (2) |
| cholesteryl (1) | −78 | $PhCH_2Cl$ (1) |
| *i*-Pr (1.6) | −78 | PhCHO (1.5) |
| *i*-Pr (1.6) | −98 | PhCHO (1.5) |
| *i*-Pr (1.5) | −78 | PhCHO (1.5)[a] |
| i-Pr (1.5) | −98 | PhCHO (1.5)[a] |
| *t*-Bu (1.2) | −98 | PhCHO (1.5) |
| *i*-Pr (2) | −78 | $Ph_2C=O$ (5)[b] |
| *i*-Pr (2) | −98 | $Ph_2C=O$ (5)[b] |

a) A mixture of **20** and PhCHO was added to ArLi. b) **20** was added to a mixture of ArLi and $Ph_2C=O$.

$$HC(=O)(OR) + ArLi \longrightarrow \underset{\mathbf{20}}{}$$

$$ArCHO + ArH + [^-C(=O)(OR)] \longrightarrow CO + RO^- \quad (\mathbf{19})$$

## Experimental

Melting points are uncorrected. $^1H$ NMR spectra were measured in $CDCl_3$ with a JEOL FX-90Q spectrometer at 90 MHz using tetramethylsilane as an internal standard. The mass spectra were recorded with a JEOL JMS-D300 mass spectrometer. Preparative liquid chromatography (PLC) was carried out using JAI Gel 1H column (Japan Analytical Industry) with chloroform as solvent. All reactions were carried out under argon.

The "usual work-up" refers to quenching with aqueous ammonium chloride, extraction with ether, washing with water, drying over anhydrous magnesium sulfate, and evaporation. The "chromatographic purification" refers to separation by column chromatography (silica gel, hexane) and subsequent purification of each fraction by PLC.

***O*-Cholesteryl Chalcogenoformate-*d*.** *O*-Cholesteryl formate-*d* (**2**): Colorless needles (ethanol–methanol), mp 98.3—98.8 °C (lit,[7] mp 97 °C for its protium analog); $^1H$ NMR δ=0.68—2.46 (43H, m), 4.48—4.96 (1H, m), 5.31—5.48 (1H, br d), and 8.02 (trace, HC(=O)); *O*-cholesteryl thioformate-*d* (**3**): Pale yellow needles (ethanol), mp 132.5—133.5 °C (lit,[2] mp 124—126 °C for its protium analog); $^1H$ NMR δ=0.69—2.58 (43H, m), and 4.99—5.75 (2H, m); *O*-3α-deuteriocholesteryl selenoformate (**6**) was prepared using 3α-deuteriocholesterol[8,9] by the Barton's method[2]: Orange crystals (hexane), mp 129.5—131.5 °C (lit,[2] mp 126—128 °C for its protium analog).

**Reaction of *O*-Cholesteryl Formate-*d* (2) with 2,4,6-Tri-*t*-butylphenyllithium (ArLi).** ArLi was prepared from 1-bromo-2,4,6-tri-*t*-butylbenzene[13] (151.4 mg, 0.465 mmol) by treatment with *t*-BuLi (2 equiv) in THF (5 ml) at −78 °C. To this ArLi was added **2** (0.232 g, 0.557 mmol) in THF (2 ml) at −78 °C. The mixture was allowed to warm to room temperature. The usual work-up and chromatographic purification gave ArCDO (**9**, 3.6 mg, 3%) and a mixture of ArD and ArH (98.4 mg, 86%). The ratio of ArD/ArH was (41.0±0.2)/(59.0±0.2) ($n$=7) as determined by its mass spectra (20 eV). **9**: Colorless crystals (methanol), mp 195.2—197.0 °C; $^1H$ NMR δ=1.33 (9H, s, *p*-*t*-Bu), 1.37 (18H, s, *o*-*t*-Bu), 7.37 (2H, s, arom.), and 11.13 (trace, CHO); MS $m/z$ (rel intensity) 275 ($M^+$, 24), 260 (100), 242 (46), 218 (30), and 57 (83).[14]

**Reaction of *O*-Cholesteryl Thioformate-*d* (3) with ArLi.** ArLi was prepared from ArBr (172.6 mg, 0.531 mmol) by treatment with *t*-BuLi (2 equiv) in THF (5 ml) at −78 °C. To this ArLi was added **3** (273 mg, 0.632 mmol) in THF (2 ml) at −78 °C. The mixture was stirred for 10 min at −78 °C and allowed to warm to room temperature. The usual work-up and chromatographic purification gave ArCDS (**10**, 56.8 mg, 37%) and a mixture of ArD and ArH (66.8 mg, 51%). The ratio of ArD/ArH was (21.5±0.9)/(78.5±0.9) ($n$=9) by its mass spectra (20 ev). **10**: Purple crystals (methanol under $N_2$), mp 154.7—155.0 °C; $^1H$ NMR δ=1.33 (9H, s, *p*-*t*-Bu), 1.37 (18H, s, *o*-*t*-Bu), and 7.38 (2H, s,

arom); MS *m/z* (rel intensity) 291 ($M^+$, 34), 276 (10), 258 (19), 235 (40), 234 (44), 220 (30), 202 (15), 179 (15), 87 (25), and 57 (100).[15]

**Reaction of *O*-Cholesteryl Selenoformate-*d* (4) with ArLi.** ArLi was prepared from ArBr (201.4 mg, 0.619 mmol) and *t*-BuLi (2 equiv) at −78 °C. To this ArLi was added **4**[1] in THF (3 ml) at −78 °C. The mixture was allowed to warm to 60 °C and stirred at this temperature for 20 h. The usual work-up and chromatographic purification afforded 6,8-di-*t*-butyl-1-deuterio-3,4-dihydro-4,4-dimethyl-1*H*-2-benzoselenin (**11**, 4.4 mg, 2%), ArCDO (26.5 mg, 16%), $ArCDHSe_nCDHAr$[14] (48.6 mg; **12**, 8% and **13**, 14% from $^1H$ NMR), $(ArSe)_2$[1] (trace), and a mixture of ArD and ArH (53.7 mg, 35%). The ratio of ArD/ArH was (5.8±0.1)/(94.2±0.1) ($n$=5) by its mass spectra (20 ev). **11**: $^1H$ NMR $\delta$=1.32 (9H, s, *t*-Bu), 1.47 (9H, s, *t*-Bu), 1.53 (6H, s, $SeCH_2C(C\underline{H}_3)_2$), 2.76 (2H, s, $SeC\underline{H}_2C(CH_3)_2$), 4.01 (1H, br s, benzyl), and 7.35 (2H, s, arom); MS *m/z* (rel intensity) 339 ($M^+$, 37), 324 (18), 282 (19), 245 (10), 230 (20), and 57 (100). Found: *m/z* 339.1570. Calcd for $C_{19}H_{29}D^{80}Se$: M, 339.1573.[14]

**Reaction of *O*-Cholesteryl Selenoformate (5) with ArLi in THF-$d_8$.** THF-$d_8$ (Merck, 99%) was dried over sodium-potassium alloy[16] before use. ArLi was prepared from ArBr (81.4 mg, 0.250 mmol) and *n*-BuLi (1.2 equiv.) in THF-$d_8$ (2 ml) at −78 °C. To this ArLi was added **5**[2] (147.1 mg, 0.308 mmol) at −78 °C. After stirring for 30 min, methanol was added for quenching to the reaction mixture at −78 °C. The usual work-up and chromatographic purification gave a mixture of ArD and ArH (22.7 mg, 37%). The ratio of ArD/ArH was (2.6±0.4)/(97.4±0.4) ($n$=8) by its mass spectra (20 ev).

**Reaction of *O*-3α-Deuteriocholesteryl Selenoformate (6) with ArLi.** ArLi was prepared from ArBr (256.6 mg, 0.789 mmol) and *t*-BuLi (2 equiv) in THF (13 ml) at −78°C. To this ArLi was added **6** (413.8 mg, 0.865 mmol) in THF (4 ml) at −78 °C. The mixture was allowed to warm to 60 °C and stirred at this temperature for 20 h. The usual work-up and chromatographic purification gave ArH (73.4 mg, 38%), 2,6-di-*t*-butyl-3,4-dihydro-4,4-dimethyl-1*H*-2-benzoselenin (23.8 mg, 9%),[1] $ArCH_2Se_nCH_2Ar$ (70.0 mg; $n$=2, 9% and $n$=3, 9% from $^1H$ NMR)[1] and ArCHO (4.8 mg, 2%). No deuterium was introduced to the products by their mass and/or $^1H$ NMR spectra.

**Attempted Trapping of Anion 19.** ArLi was prepared from ArBr (1 mmol) and *n*-BuLi (1.2 equiv) in THF at −78 °C. To this ArLi was added formate **20** and a quencher under the conditions described in Table 2. The usual work-up gave only a mixture of ArCHO and ArH by its $^1H$ NMR spectra.

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