# A convenient synthesis of unsymmetrical organotellurides of biological interest

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# A Convenient Synthesis of Unsymmetrical Organotellurides of Biological Interest

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A method has been developed for the preparation of unsymmetrical organotellurides (R–Te–R′). Several structurally modified tellurium fatty acids have been prepared in good overall yields (32–43%) by reaction of an equivalent of $Na_2Te/H_2O$ and 0.5 equiv each of RX and R′X in THF/EtOH. This single-vessel rapid synthesis is an improvement over existing synthetic methods for the preparation of unsymmetrical dialkyl tellurides since it appears to be a general route for the synthesis of a variety of multifunctional unsymmetrical tellurides. This method can also be applied to selenium as a general method for the preparation of multifunctional unsymmetrical dialkyl selenides.

## Introduction

Radiolabeled organotellurium compounds such as long-chain fatty acids,[1] steroids,[2] and amino acids[3] have attracted considerable interest during the past few years as agents with important applications in nuclear medicine.[4] The most extensively investigated class of agents containing tellurium are the $^{123m}Te$-labeled long-chain fatty acids which have important potential applications for the early detection of heart disease using external nuclear medicine imaging techniques.[5] Tissue distribution studies in laboratory animals with 9-[$^{123m}Te$]telluraheptadecanoic acid (9-THDA) have demonstrated the prolonged retention of radioactivity in the heart tissue (myocardium).[5] The introduction of the tellurium heteroatom to the fatty acid chain has thus been shown to represent a unique means of trapping the fatty acid in the myocardium.

A variety of synthetic routes to symmetrical dialkyl tellurides are available. The most generally used methods for the preparation of symmetrical tellurides (R–Te–R) employ sodium telluride (Na–Te–Na) and tellurium tetrachloride ($TeCl_4$) and proceed via a coupling reaction of Na–Te–Na or $TeCl_4$ with an organic or organometallic reagent, respectively.[6] On the other hand, relatively few convenient syntheses of unsymmetrical dialkyl tellurides (R–Te–R′) have been reported. This is partly due to the difficulty encountered in handling alkyl tellurides. These agents are often photosensitive and air sensitive which requires handling under an inert atmosphere and red lights. In addition, the known methods of synthesis of unsymmetrical dialkyl tellurides often require tedious manipulations and lack the scope for the preparation of a variety of multifunctional tellurides.

One approach for the preparation of unsymmetrical dialkyl tellurides involves the thermal decomposition of telluronium halides[7] (Scheme I). Unfortunately, this method suffers from low yields and is of limited scope since it appears to be applicable only for the preparation of α-keto tellurides. The overall yield of the ethyl 3-telluraheptanoate by this method was 16% based on tellurium metal and 8% based bromide.[7] bromide.[7] A more recently developed synthetic route for the preparation of unsymmetrical reagent.[8,9] utilizes an alkyllithium reagent.[8,9] Tellurium metal undergoes facile insertion into organolithium reagents to form a solution of lithium alkyltellurolates, which are converted into symmetrical dialkyl tellurides by addition of alkyl halides. In this manner unsymmetrical dialkyl tellurides have been prepared in which one of the alkyl groups originated from a commerical alkyllithium reagent. This method is therefore limited only to dialkyl tellurides containing functional groups that are compatible with the formation of RLi.

### Scheme I

$$2CH_3CH_2CH_2CH_2Br + Te \rightarrow$$
$$CH_3CH_2CH_2CH_2TeCH_2CH_2CH_2CH_3 + BrCH_2CO_2Et \rightarrow$$
$$[(CH_3CH_2CH_2CH_2)_2TeCH_2COOEt]^+Br^- \xrightarrow{\Delta}$$
$$CH_3CH_2CH_2CH_2TeCH_2COOEt$$

## Results and Discussion

The usual method used to prepare unsymmetrical tellurium compounds of biological interest such as 9-THDA involves the initial formation of the symmetrical dialkyl ditellurides (R–Te–Te–R, Scheme II). Although a variety of unsymmetrical tellurium fatty acids have been obtained by this route, the yields are only modest (10–20%) because the R–Te–Na species is used in excess to ensure complete consumption of the R′X substrate. This strategy is required because of the difficulties often encountered in the chromatographic separation of the R′X [$Br-(CH_2)_7COOCH_3$] and R–Te–R′ [$CH_3(CH_2)_7-Te-(CH_2)_7-COOCH_3$] components. With use of the R–Te–Na in excess, subsequent atmospheric exposure of the reaction mixture produces rapid oxidation of the tellurol (R–Te–Na) to the

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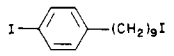
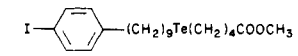
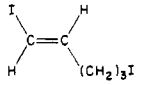
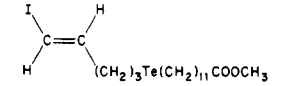
Table I. Yields of Unsymmetrical Tellurides Prepared as Described in Scheme III

| RX | R′X | fatty acid ester[a] | compd | yield,[b] % |
|---|---|---|---|---|
| $CH_3(CH_2)_7Br$ | $Br(CH_2)_7COOCH_3$ | $CH_3(CH_2)_7Te(CH_2)_7COOCH_3$ | 1 | 39 |
|  | $I(CH_2)_4COOCH_3$ |  | 2 | 43 |
|  | $I(CH_2)_{11}COOCH_3$ |  | 3 | 32 |
| $CH_3(CH_2)_3Br$ | $Br(CH_2)_{11}COOCH_3$ | $CH_3(CH_2)_3Te(CH_2)_{11}COOCH_3$ | 4 | 39 |
| $HC{\equiv}C(CH_2)_3I$ | $I(CH_2)_{11}COOCH_3$ | $HC{\equiv}C(CH_2)_3Te(CH_2)_{11}COOCH_3$ | 5 | 35 |

[a] Satisfactory infrared, proton nuclear magnetic resonance, mass spectral, and elemental analyses (±0.4% for C and H) were obtained for the free acids of compounds 1-5. [b] Yields are based on isolated products.

symmetrical R–Te–Te–R species which is readily separated by column chromatography.

### Scheme II

$$Na + Te \xrightarrow[\text{or Te–NaH}]{\text{Te–Na/liq NH}_3} Na\text{–Te–Te–}Na \xrightarrow{RX} R\text{–Te–Te–}R \xrightarrow{NaBH_4} R\text{–Te–}Na \xrightarrow{R'\text{–}X} R\text{–Te–}R'$$

Recently, it was reported that sodium borohydride rapidly reduces tellurium metal to sodium tellurol, Na–Te–H, in $H_2O$ at 80 °C.[10] As a result of our interest in preparing a variety of modified radiolabeled tellurium fatty acid analogues for structure-activity studies, we have investigated the use of Na–Te–H for the synthesis of unsymmetrical organotellurides. In this study we report a rapid and convenient single reaction flask method for the preparation of unsymmetrical tellurium fatty acid esters in good yields (32–43%).

Our initial studies involved the sequential addition of the RX and R′X substrates to a solution of NaTeH. For example, an aqueous solution of Na–Te–H at pH 8 was treated with 0.5 equiv of RX in a 1:1 mixture of THF/EtOH at room temperature. Following adjustment of the solution to pH 10 and subsequent addition of 0.5 equiv of R′X in a 1:1 mixture of THF/EtOH, only the symmetrical products R–Te–R and R′–Te–R′ were isolated. However, when 0.5 equiv of each halogenated substrate was added simultaneously to an aqueous solution of Na–Te–Na, good yields of unsymmetrical tellurium products were obtained.

The strategy for adding 0.5 equiv of each substrate simultaneously is based on the supposition that if the two substrates have the same reactivity with Na–Te–Na, one would expect the product ratio shown in Scheme III. By this procedure an equal amount of each substrate would always be available for nucleophilic attack by Na–Te–Na. This reaction has been found to work quite well with iodinated and brominated substrates. The symmetrical R–Te–R and R′–Te–R′ byproducts are readily removed by chromatography, and consistent yields (~40%) of the desired unsymmetrical R–Re–R′ products have been obtained. The isolated yields for the syntheses of a series of esters are summarized in Table I.

### Scheme III

$$Te + NaBH_4 \rightarrow Na\text{–Te–}Na \xrightarrow[R'\text{–}X]{R\text{–}X} \underset{\sim 25\%}{R\text{–Te–}R} + \underset{\sim 50\%}{R\text{–Te–}R'} + \underset{\sim 25\%}{R'\text{–Te-}R'}$$

This 2-h single reaction vessel synthesis is rapid, and the radiation exposure to personnel is greatly reduced when compared to the longer (~8 h) two-step method (Scheme II). The overall yields are good and the reaction conditions are mild, which suggests that this may be a general route for the synthesis of a variety of multifunctional unsymmetrical organotellurides. This route is also compatible with the short half-life (7.2 h) of $^{73}Se$ and can be extended to the preparation of a wide variety of $^{73}Se$-labeled radiopharmaceuticals. The synthesis of a variety of multifunctional unsymmetrical selenides using this rapid method is now under investigation.

Table II. Proton Nuclear Magnetic Resonance (δ) of Unsymmetrical Tellurides

| compd | |
|---|---|
| 1 | 0.90 (t, $J$ = 6 Hz, 3 H, $CH_2CH_3$), 2.33 (t, $J$ = 6 Hz, 2 H, $CH_2COOCH_3$), 2.62 (t, $J$ = 6 Hz, 4 H, $CH_2TeCH_2$), 3.61 (s, 3 H, $COOCH_3$) |
| 2 | 2.27 (t, $J$ = 7 Hz, 2 H, $CH_2COOCH_3$), 2.56 (t, $J$ = 7 Hz, 6 H, $CH_2TeCH_2$ and $CH_2Ph$), 3.61 (s, 3 H, $COOCH_3$), 7.19 (AA′BB′, $J$ = 7 Hz, 4 H, aromatic) |
| 3 | 2.34 (t, $J$ = 6 Hz, 2 H, $CH_2COOCH_3$), 2.64 (t, $J$ = 6 Hz, 4 H, $CH_2TeCH_2$), 3.67 (s, 3 H, $COOCH_3$), a complex multiplet at 5.85-6.85 (2 H, $ABX_2$, $ICH{=}CHCH_2$) |
| 4 | 0.90 (t, $J$ = 6 Hz, 3 H, $CH_2CH_3$), 2.35 (t, $J$ = 6 Hz, 2 H, $CH_2COOCH_3$), 2.56 (t, $J$ = 6 Hz, 4 H, $CH_2TeCH_2$), 3.65 (s, 3 H, $COOCH_3$) |
| 5 | 1.87 (m, 1 H, C=C$H$), 2.35 (t, $J$ = 6 Hz, 2 H, $CH_2COOCH_3$), 2.60 (t, $J$ = 6 Hz, 4 H, $CH_2TeCH_2$), 3.66 (s, 3 H, $COOCH_3$) |

Table III. Elemental Analyses

| compd | calcd | found |
|---|---|---|
| 9-telluraheptadecanoic acid (1) | C, 50.13 | 50.38 |
| | H, 8.36 | 8.37 |
| 15-(*p*-iodophenyl)-6-tellurapentadecanoic acid (2) | C, 43.03 | 43.19 |
| | H, 5.60 | 5.69 |
| 18-iodo-13-tellura-17-octadecenoic acid (3) | C, 39.02 | 39.18 |
| | H, 5.99 | 6.07 |
| | I, 24.32 | 24.24 |
| 13-telluraheptadecanoic acid (4) | C, 50.13 | 50.09 |
| | H, 8.16 | 8.39 |
| 13-tellura-17-octadecynoic acid (5) | C, 51.91 | 51.70 |
| | H, 7.63 | 7.82 |

## Experimental

**General Data.** All chemicals and solvents were analytical grade and were used without further purification. Column chromatography was performed with acidic grade silicic acid, 60–200 mesh (Sigma Chemical Co.). The melting points were determined in open capillary tubes using a Buchi SP apparatus and are uncorrected. The thin-layer chromatographic analysis (TLC) were performed by using 250-μm thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). The low-resolution mass

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spectra (MS) were recorded by using a Kratos MS-25 low-resolution instrument under the following conditions: ionizing energy, 70 eV; accelerating potential, 8000 V; trap current, 100 μA; probe temperature, 200–300 °C. The proton nuclear magnetic resonance spectra ($^1$H NMR) were obtained at 60 MHz with a Varian 360-A instrument or at 200 MHz with a Nicolet high-resolution instrument. Samples (30–40 mg) were dissolved in the solvents indicated, and resonances are reported downfield (δ) from the internal tetramethylsilane standard. Elemental analyses were carried out at Galbraith Laboratories, Knoxville, TN. Unless otherwise indicated, the tellurium compounds were handled under red lights and inert atmosphere to minimize photochemical decomposition or autoxidation.

**Methyl 9-Telluraheptadecanoate. General Procedure.** A mixture of tellurium metal (127 mg, 1 mmol) and 3 mL of distilled $H_2O$ was deaerated and heated at 80 °C in a oil bath under red lights and an argon atmosphere. An argon purged aqueous (1 mL) solution of $NaBH_4$ (100 mg) was added dropwise until a clear, colorless solution of Na–Te–Na was obtained.[11] The mixture was then cooled to room temperature, and 15 mL of an argon purged 1:1 mixture of THF/EtOH containing methyl 8-bromooctanoate (223 mg, 0.95 mmol) and 1-bromooctane (202 mg, 1.05 mmol) was added. The solution was stirred for 60 min under an argon atmosphere, poured into 150 mL of $H_2O$, and then extracted with three 50-mL portions of ethyl ether. The ether extracts were washed with $H_2O$ (3 × 50 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was dissolved in petroleum ether (30–60 °C) and chromatographed on a silicic acid (25 g) column slurried in petroleum ether. The column was initially eluted with ten 25-mL fractions of petroleum ether followed by ten 25-mL fractions of $C_6H_6$. Aliquots of the fractions were monitored by TLC (solvent $C_6H_6$), and fractions 13–16 were combined to afford (39%) of methyl 9-telluraheptadecanoate as an oil, TLC, $R_f$ 0.50 ($C_6H_6$).

(11) As the Te begins to dissolve, the solution initially turns a deep purple or red resulting from the initial formation of sodium ditelluride, Na–Te–Te–Na. As additional Te metal dissolves, the solution becomes progressively lighter until a colorless solution of Na–Te–Na is formed.

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**Registry No.** 1, 84057-03-4; 2, 81815-28-3; 3, 86374-37-0; 4, 86374-38-1; 5, 85976-76-7; Te, 13494-80-9; Na–Te–Na, 12034-41-2; $Br(CH_2)_7CH_3$, 111-83-1; $Br(CH_2)_7COOCH_3$, 26825-92-3; Na–Te–Te–Na, 11089-53-5; $p$-$IC_6H_4(CH_2)_9I$, 86374-34-7; $CHI{=}CH(CH_2)_3I$, 86374-35-8; $CH_3(CH_2)_3Br$, 109-65-9; $CH{\equiv}C(CH_2)_3I$, 2468-55-5; $I(CH_2)_4COOCH_3$, 14273-88-2; $I(CH_2)_{11}COOCH_3$, 86374-36-9; $Br(CH_2)_{11}COOCH_3$, 26825-95-6.

# Substituent Effects in Cluster Species.[1] 4. Ultraviolet–Photoelectron Spectroscopic and Molecular Orbital Studies of Carbyne Complexes of Multinuclear Cobalt Carbonyls

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The perturbation of carbyne fragments on being bound to one, two, and three nearest-neighbor cobalt atoms is examined experimentally and theoretically. The former approach results from the development of a photoelectron spectroscopic probe based on the ionization properties of a benzene ring. The latter utilizes Fenske–Hall nonparameterized quantum chemical calculations to analyze the bonding. Both approaches are applied to known carbyne complexes of multinuclear cobalt carbonyls while the latter is also applied to analogous complexes without carbonyl ligands. The two methods give congruent pictures of ligand properties as a function of number of metal atom interactions. A specific conclusion is that the negative charge on a carbyne carbon increases as the number of nearest-neighbor cobalt atoms increases. The implications of this result with respect to carbyne binding to metal surfaces are discussed.

The structure and bonding in transition-metal clusters have been of intense interest to inorganic chemists for some time.[2] An expression of this interest is the on-going search for ligand binding in multinuclear metal systems that differs qualitatively from the binding of the ligand in mononuclear systems. Just as cagelike polyboranes exhibit significantly different properties from monoboranes,[3] so too one expects significant differences in polymetallic clusters relative to mononuclear complexes. In this work we measure the perturbation of ligands bound to multinuclear metal sites as a function of the number of metal–ligand interactions.

The construction of bonding models for multinuclear transition-metal systems is hindered by the sheer size of the problem.[2] On the one hand the strictly calculational approach obscures the solution in a welter of approximate detail,[4] whereas the experimental approach of spectroscopy suffers interpretational problems[5] and is not sufficiently detailed. We have chosen, therefore, to focus attention on the variation of a selected number of parameters through a series of closely related, geometrically characterized

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(4) Semiempirical methods of the extended Hückel type are much used in this area.
(5) For example, a bonding model is often used to assign an observed photoelectron spectrum, and, thus, the latter yields no direct information on the bonding.

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