Unexpected ethyltellurenylation of epoxides with elemental tellurium under lithium triethylborohydride conditions

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Abstract: The one-pot multistep ethyltellurenylation reaction of epoxides with elemental tellurium and lithium triethylborohydride has been described. The reaction mechanism has been experimentally investigated. Lithium ditelluride and triethyl borane, formed from elemental tellurium and lithium triethylborohydride, were shown to be the key species involved in the reaction mechanism. Epoxides undergo ring-opening reaction with lithium ditelluride to afford \(\beta\)-hydroxy ditellurides, which are sequentially converted into the corresponding \(\beta\)-hydroxy-alkyl-ethyltellurides by transmetalation with triethyl borane, reasonably proceeding through \(\text{Sn}_2\) mechanism.

Keywords: tellurium; tellurides; ditellurides; superhydride; boranes; ring-opening-reactions; epoxides; transmetallation; radicals.

1. Introduction

Organoselenium [1,2] and organotellurium [3] compounds continue to find wide application in chemical sciences and biology [4-8]. Tellurium-containing derivatives play an important role in organic synthesis [3,9], materials sciences [10,11], and medicinal chemistry [8,12-15]. The incorporation of tellurium atoms into organic structures is often a rewarding strategy in developing new enzyme modulators [14-17], catalysts [18], smart materials [10,11], and glutathione-peroxidase-like antioxidants [19-25]. Additionally, often undergoing regio- and stereo-selective transformations, organotellurium compounds can be employed in synthetically useful functional group conversion reactions [26,27] and carbon-carbon bond-forming processes.[28-30] Owing to these features, tellurenylation reactions provide an attractive functional handle for further elaboration. The development of new, reliable, and general methodologies towards these chalcogen-containing organic molecules is thus highly sought after in organic synthesis. Particularly, the possibility to access densely functionalised and \(\text{sp}^3\)-rich compounds, characterised by high molecular complexity, enables the possibility to define and explore new chemical space and plays a key role in terms of successfully developing new catalysts and drug candidates [31,32]. Furthermore, \(\text{sp}^3\)-rich organochalcogens bearing O- and N-containing functionalities have been demonstrated to possess improved catalytic and pharmacological properties [15-17,20,23]. However, although a number of methods towards selenides and tellurides have been reported, a number of limitations remained, including functional-group compatibility and the harsh reaction conditions. Therefore, the development of mild procedures for the synthesis of densely functionalised molecules still remains challenging.
Three-membered heterocycles such as epoxides and aziridines, often undergoing regioselective nucleophilic ring-opening reactions (NRORs), represent convenient starting materials for the synthesis of functionalised chalcogen-containing systems [33]. A number of ring-opening-based procedures towards hydroxy- and amino-substituted selenides and tellurides have been developed over the last decade [34-39]. Such a functionalised chalcogenides have also been employed as intermediates for the synthesis of valuable compounds [40,41] and as organocatalysts for the asymmetric addition of diethylzinc to aldehydes [42].

In this communication, as a part of our growing interest in the study of the chemistry of organotellurium compounds, we report a study on the mechanism of an unexpected reaction of epoxides with elemental tellurium and lithium triethylborohydride, leading to the formation of \( \beta \)-hydroxy-alkyl-ethyl-tellurides.

### 2. Results

During the course of our studies on the reactivity of strained heterocycles with selenium-centered nucleophiles we developed convenient routes towards a variety of hydroxy-, amino-, and mercapto-substituted Se-containing systems [43-45]. For example, through the tuning of the stoichiometry and the conditions of the reaction of (Me\(_3\)Si)\(_2\)Se [(bis(trimethylsilyl)selenide, a synthetic equivalent of hydrogen selenide] with epoxides, thiiranes, and aziridines, we were able to successfully achieve a range of functionalised selenols [43], selenides, and diselenides [46].

Attracted by the synthetic utility and versatility of organotellurium compounds, we recently moved to evaluate the chemistry of tellurium-centered nucleophiles with strained heterocycles [47,48]. The poor stability of (Me\(_3\)Si)\(_2\)Te [49] prompted us to employ lithium telluride and lithium ditelluride, generated from elemental tellurium and lithium triethylborohydride (superhydride), as tellurenylation reagents for the NRORs of epoxides and aziridines [48]. However, while ring opening of epoxides with LiTe provided access to symmetrical \( \beta \)-hydroxy-tellurides 1 (Scheme 1, part a), the reaction with Li\(_2\)Te gave almost exclusively ethyl-alkyl-tellurides 2 instead of the expected \( \beta \)-hydroxy-ditellurides 3, which were isolated only in traces amount (Scheme 1, part b).

Intrigued by this result, we wished to deeper investigate such a transformation in order to establish the mechanism involved in the formation of unsymmetrical hydroxy-ethyl-tellurides 2.

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\text{Scheme 1. Reactivity of epoxides with LiTe and Li}_2\text{Te, generated from elemental tellurium under lithium triethylborohydride conditions. } a, \text{ Synthesis of tellurides 1. } b, \text{ Unexpected formation of ethyl-alkyl-tellurides 2.}
\]

A plausible explanation for the formation of unsymmetrical tellurides 2 involves the transmetalation of triethylborane with \( \beta \)-hydroxy-ditellurides 3. However, an alternative path could proceed through the ring-opening of epoxides with tris(ethyltelluro)borane 4 which, in principle, could be generated from lithium ditelluride and triethyl borane. A series of control experiments were therefore undertaken in order to test these hypotheses.

We initially evaluated whether tris(ethyltelluro)borane 4 could be generated upon treatment of elemental tellurium with lithium triethylborohydride. However, the formation of 4 was not observed under the standard reaction conditions (Scheme 2, reaction a). Traces of 4 were detected neither performing the reaction in a coaxial NMR tube and monitoring its progress over the time.
On the basis of these results, we next turned our attention to evaluating whether under the studied conditions ditellurides 3 could behave as precursors of tellurides 2. We recently developed an on water methodology to access functionalised dialkyl ditellurides from elemental tellurium, sodium hydroxymethanesulfinate, and strained heterocycles [50]. Therefore, we employed this route to prepare β-hydroxy-ditellurides and then we studied their reactivity with organoboranes.

β-Hydroxy-ditelluride 3a was thus treated with lithium triethylborohydride and, pleasingly, β-hydroxy-ethyl-alkyl-telluride 2a was formed in 42% yield (Scheme 2, reaction b). However, under these conditions the alkyltellurolate 5a, arising from the LiBEt 3H-induced reduction of the ditelluride 3a, could be the species actually involved in the formation of 2a. Unequivocal proof for the direct involvement of ditelluride 3a and triethylborane was obtained by the reaction of these two compounds which, in absence of hydrides, afforded 2a in 48% yield (Scheme 2, reaction c). Notably, related diselenide 6a reacted slowly with triethylborane under the same conditions and only traces of unsymmetrical ethyl-selenide 7a were detected after 6 h (Scheme 2, reaction d).

Trialkyl boranes readily undergo radical reactions generating alkyl radicals. Such processes can be initiated by oxygen, light or radical initiators, such as AIBN [51]. Additionally, ditellurides have been demonstrated to easily react with alkyl radicals, exhibiting remarkable radical-trapping activity [52]. On the basis of these considerations and supported by a literature precedent describing the reactivity of diphenyl ditelluride with organoboranes [53], we hypothesised a radical process involving ditellurides 3 and ethyl radicals. Control experiments performed using BHT (3,5-di-tert-butyl-4-hydroxytoluene) as a radical inhibitor further demonstrated a radical pathway. Additionally, performing reactions b and c (Scheme 2) in the dark had no significant effect on the reaction outcome, showing that the light was not required for the process leading to 2a.

On the basis of the control experiments and of precedent reports, a proposed reaction mechanism is reported in the Scheme 3. The first step (I) involves the reduction of elemental tellurium with lithium triethylborohydride, leading to the formation of lithium ditelluride and triethylborane. Subsequently (II), Li2Te2 reacts with two equivalents of epoxide to afford the corresponding ditelluride 3 through a regioselective nucleophilic ring-opening-reaction. The following transmetalation of Et3B with 3 reasonably proceeds through the oxygen-mediated formation of ethyl radicals (III) which, in turn, react with the ditelluride 3 providing the unsymmetrical hydroxyl-ethyl-telluride 2 through an Si2 process (IV) [54,55]. The tellurium-centered radical 8, formed in the Si2 reaction, undergoes typical propagation and termination processes, including the recombination with a second equivalent of 8 providing
ditelluride 3 [56]. Furthermore, the reaction of 8 with oxygen or borylperoxyl radicals (V) would afford reactive tellurenyl peroxides which plausibly decompose, thus explaining the rather low yield of the transmetalation reaction and the absence of ditelluride 3, or unreacted epoxide in the crude mixture.

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\text{(I)} \quad 2\text{Te} \xrightarrow{H_2} \text{Li}_2\text{Te}_2
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\[
\text{(II)} \quad 2\text{Et}_3\text{B} \xrightarrow{\text{Et}_2\text{BOO}^-} \text{TeO}_2\text{Et}_2
\]

\[
\text{(III)} \quad \text{O}_2 \xrightarrow{\text{Et}_2\text{BOO}^-} \text{R}_2\text{TeOH}
\]

\[
\text{(IV)} \quad \text{R}_2\text{TeOH} \xrightarrow{\text{LiBEt}_3\text{H}} \text{Li}_2\text{Te}_2
\]

\[
\text{(V)} \quad \text{Te} \xrightarrow{\text{R}_2\text{TeOH}} \text{R}_2\text{Te}_2\text{OH}
\]

**Scheme 3.** Proposed mechanism for the formation of unsymmetrical hydroxy-ethyltellurides 2.

### 3. Conclusions

In conclusion, we have described a one-pot multistep reaction in which epoxides are converted into the corresponding unsymmetrical β-hydroxy-ethyltellurides upon treatment with elemental tellurium under lithium triethylborohydride reducing conditions. The reaction mechanism has been experimentally investigated; β-hydroxy ditellurides and triethyl borane were demonstrated to be the key species involved in this one-pot ethyltellurenylation reaction. The transmetalation of triethyl borane with hydroxy-dialkyl-ditellurides, reasonably occurring through an oxygen-induced S2 mechanism, represents the key step of the process. The findings here described can be exploited for the development of novel general methodologies towards the synthesis of synthetically and biologically valuable complex sp3-rich unsymmetrical tellurides. Further studies on the application of this reaction to functionalised boranes (and boronic esters) for the preparation and the elaboration of poly-functionalised unsymmetrical tellurides are currently on-going in our laboratories.

### 4. Materials and Methods

**4.1 Experimental Section**

All reactions were carried out in an oven-dried glassware. Solvents were dried using a solvent purification system (Pure-Solv™). All commercial materials were purchased from various commercial sources and used as received, without further purification. Flash column chromatography purifications were performed with Silica gel 60 (230-400 mesh). Thin layer chromatography was performed with TLC plates Silica gel 60 F254, which was visualised under UV light, or by staining with an ethanolic acid solution of p-anisaldehyde followed by heating. High resolution mass spectra (HRMS) were recorded by Electrospray Ionization (ESI).

\(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra were recorded in CDCl3 with Mercury 400, Bruker 400 Ultrashield, and Varian Gemini 200 spectrometers operating at 400 MHz for \(^1\text{H}\) and 100 MHz for \(^{13}\text{C}\). NMR signals
were referenced to nondeuterated residual solvent signals: 7.26 ppm for $^1$H and 77.0 ppm for $^{13}$C. 

$^{125}$Te NMR spectra were recorded in CDCl$_3$ at 126 MHz with a Bruker Ultrashield 400 Plus instrument. (PhTe)$_2$ was used as an external reference ($\delta = 420$ ppm). Chemical shifts ($\delta$) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. $^1$H NMR data are reported as follows: chemical shift, integration, multiplicity ($s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $m$ = multiplet, $dd$ = doublet of doublet, $bs$ = broad singlet, ecc.), coupling constant (J), and assignment.

Ditelluride 3a [50] and diselenide 6a [46] were prepared from 2-((benzyloxy)methyl)oxirane according to literature reported procedures.

4.2 General Procedure for the synthesis of $\beta$-hydroxy-alkyl-ethyl-tellurides 2

Li$_2$Te was generated according to literature [49] from 1.0 mL of a 1 M THF solution of LiEt$_3$BH (1.0 mmol, 1.0 eq.) and elemental tellurium powder (128 mg, 1.0 mmol, 1.0 eq.), stirred at ambient temperature under inert atmosphere (N$_2$) for 6 h. The dark red suspension of Li$_2$Te in THF was treated with the epoxide (1.0 mmol, 1.0 eq.) and the reaction was stirred for 6 h at ambient temperature. Afterwards, the mixture was diluted with Et$_2$O (10 mL), filtered through a short pad of celite, washed with sat. aq. NH$_4$Cl and then with H$_2$O (2 x 5 mL). The organic phase was dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The crude residue was then purified by flash chromatography to yield $\beta$-hydroxy-alkyl-ethyl-tellurides 2.

4.2.1 Synthesis of 1-(Benzyloxy)-3-(ethyltellanyl)propan-2-ol 2a

According to the general procedure, 2-((benzyloxy)methyl)oxirane (152 µL, 1.0 mmol) and elemental tellurium (128 mg, 1.0 mmol) gave after flash chromatography (Et$_2$O/petroleum ether 1:1) 2a as a colourless oil (61 mg, 38%). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ (ppm) 1.60 (3H, t, $J = 7.6$ Hz, CH$_3$), 2.63 (2H, ap q, $J = 7.6$ Hz, CH$_3$C$_6$H$_2$Te), 2.63 (1H, bs, OH), 2.76-2.89 (2H, m, CH$_2$Te), 3.41-3.48 (1H, m, C$_2$H$_4$H$_2$O), 3.59 (1H, dd, $J = 4.2, 9.6$ Hz, CH$_2$H$_2$O), 3.45-3.97 (1H, m, CH$_2$O), 4.55 (2H, ap s, CH$_2$Ph), 7.26-7.40 (5H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) -4.5(CH$_3$C$_6$H$_2$Te), 7.7 (CH$_2$Te), 17.8, 70.6, 73.4, 74.3, 127.8, 127.8, 128.4, 137.9. $^{125}$Te NMR (126 MHz, CDCl$_3$): $\delta$ (ppm) 213.6.

Conflicts of Interest: The authors declare no conflict of interest.

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If regenerated, ditellurides 3 reasonably undergoes transmetalation with ethyl radicals affording \( \beta \)-hydroxy-alkyl-ethyl-tellurides 2 and radicals 8, following the proposed mechanism reported in the Scheme 3.