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γ-Butyltelluro-2-butanol: a route to reactive 1,4-dianion intermediates

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Abstract— γ -Butyltelluro-2-butanol was reacted with 2 equiv of *n*-butyllithium. Both tellurium/lithium exchange and the proton abstraction reactions took place in a single step and the lithium dianion intermediate efficiently reacted with aldehydes and ketones, producing the corresponding diols. © 2005 Elsevier Ltd. All rights reserved.

Elemental tellurium reacts with Grignard¹ or organolithium² reagents, producing the corresponding organometallic tellurolate, which react with electrophiles, leading to symmetrical and unsymmetrical tellurides.^{3–5} Organic tellurides can be transformed into the corresponding lithium derivatives through a tellurium/lithium exchange reaction.⁶ It was found that this is one of the fastest metalloid/lithium exchange reactions.⁷

Organolithium compounds are probably the most popular organometallic species, due to their excellent nucleophilic character. Their importance and versatility⁸ are not only due to their capacity to act as nucleophile or base, but also to their ability to be converted into other reactive organometallics by transmetallation. Basically, every metal more electronegative than lithium can be used for this purpose.

Aiming to develop more efficient synthetic processes based in organotellurium chemistry, we are exploring the preparation of functionalized organolithium intermediates by tellurium/lithium exchange. Recently, we have generated β -butyltelluro carbonyl compounds by the Michael addition of *n*-butyltellurol to α , β -unsaturated ketones (e.g., 1).⁹ Compound 1 was transformed into the corresponding ketal and submitted to a tellurium/lithium exchange producing the masked lithium

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homoenolate **3a**, that was reacted with benzaldehyde. The lithium intermediate **3a** was also transformed into the functionalized higher order cyanocuprate **3b** by reaction with CuCN·2LiCl and reacted with enones (Scheme 1).¹⁰

Herein we describe the chemoselective reduction of isolated telluride **1** to the corresponding γ -butyltelluro alcohol **2**¹¹ and its transformation into the 1,4-dianion intermediate **4**. Alternatively, **2** was produced in a onepot procedure by sequential Michael addition of butyltellurol to methyl vinyl ketone followed by in situ carbonyl reduction of the resulting β -butyltelluro ketone.¹² By the last procedure, the alcohol **2** was generated in 70% isolated yield.



Scheme 1. Conversion of tellurides into organometallic reactive species.

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Scheme 2. Reaction of lithium dianion with aldehydes and ketones.

Cohen reported the generation of dilithio intermediates like **4** by sequential treatment of phenylthiocarbinols with butyllithium and lithium di-*tert*-butylbiphenylide (Li-DTBB).¹³ Butyllithium promotes the deprotonation of the hydroxy unit and the pre-generated Li-DTBB performs the reductive lithiation of the phenylsulfide rest.

In this work the reactive 1,4-dianion 4 was generated in a single operation by reacting γ -butyltelluro alcohol 2 with 2 equiv of commercially available *n*-butyllithium. Both aldehydes and ketones reacted with 4 affording the corresponding diols in good yields (Scheme 2).¹⁴

Preliminary studies using equimolar amounts of both dianion **4** and the eletrophiles, afforded the desired diols **6a–f** only in moderated yields (38–63%). Substantial increases of yields were obtained by using 2 equiv of **4** relative to **5**. The 1,2-addition reaction worked very well even using ketones as the eletrophile. Diols **6a** and **b**, are analogs of 4-ipomeanol, a naturally occurring pneumotoxin under development for treatment of lung cancer.¹⁵

The diols **6a–d** were cyclized by reacting with catalytic amount of *p*-TSA in dichloromethane yielding the corresponding tetrahydrofurans (Scheme 3).¹⁶

The reaction of dianion 4 with a range of other electrophiles is under investigation in order to obtain functionalized compounds such as spiroketals and chiral diols.

The tellurides described here are stable odourless yellow oils and can be easily generated in a one-pot procedure from elemental tellurium. Dibutyltelluride produced in



Scheme 3. Cyclization reaction of diols 6a-d to the corresponding tretrahydrofurans.

the tellurium/lithium exchange step is totally compatible with all subsequent operations and can be easily removed in an odorless operation by washing of the organic phase with a diluted sodium hypochlorite solution.

In conclusion, we showed that a functionalized organolithium can be easily prepared from an organotelluride obtained from commercially available elemental tellurium, *n*-butyllithium and methyl vinyl ketone.

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- 11. Reduction of 4-(butyltelluro)butan-2-one (1) to 4-(butyltelluro)butan-2-ol (2): to a round bottomed flask were added the telluride 1 (5 mmol, 1.28 g) and ethanol (20 mL). To the resulting solution was added dropwise an ethanolic solution of NaBH₄ (5.5 mmol, 0.21 g in 6 mL ethanol). The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC.

The reaction mixture was quenched with water (50 mL) and diluted with a mixture of ethyl acetate-hexane 1:1 (50 mL). The phases were separated and the aqueous phase was extracted with a mixture of ethyl acetatehexane (1:1, 2×50 mL). The organic phases were combined, dried with magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography eluting with a mixture of hexane-ethyl acetate (15:1), to give 4-(butyltelluro)butan-2-ol (2); yield: 1.09 g, (85%); ¹H NMR: (200 MHz, CDCl₃, ppm) δ 0.85 (t, J = 7.2 Hz, 3H); 1.13 (d, J = 6.3 Hz, 3H); 1.31 (sext, J = 7.2 Hz, 2H); 1.65 (quint, J = 7.2 Hz, 2H); 1.76–1.85 (m, 2H); 2.53–2.69 (m, 4H); 3.75 (sext, J = 6 Hz, 1H); ¹³C NMR: (50 MHz, CDCl₃, ppm) δ –2.3; 2.7; 13.4; 23.2; 25.0; 34.2; 41.1; 69.1; LRMS m/z (rel. int.) 260 (M⁺+2, 13); 258 (M⁺, 13); 256 (7); 255 (3); 254 (2); 215 (3); 186 (8); 72 (5); 57 (73); 55 (100); 45 (44); ¹²⁵Te NMR (CDCl₃, 157.79 MHz/298 K/ Ph₂Te₂) δ (ppm) 251.43.

- 12. One-pot preparation of 4-(butyltelluro)butan-2-ol (2): to a flame dried two necked flask under nitrogen atmosphere were sequentially added elemental tellurium (5 mmol, 0.64 g) and THF (10 mL). Under vigorous stirring was added dropwise a solution of *n*-butyllithium (5 mmol, $3.5 \text{ mL from } 1.4 \text{ mol } \text{L}^{-1}$ hexane solution). To the resulting light yellow solution was added deoxygenated water (10 mmol, 0.18 mL). The mixture was stirred for 5 min and then methyl vinyl ketone (5 mmol, 0.35 g, 0.4 mL) was added in one portion. The resulting red mixture was stirred for 30 min and then an aqueous solution of NaBH₄ (6 mmol, 0.22 g; 6 mL of a $1 \mod L^{-1}$) was added by means of a dropping funnel. The progress of reaction was monitored by TLC then diluted with water (20 mL) and a mixture of ethyl acetate-hexane 1:1 (50 mL). The phases were separated and the aqueous phase was washed with a mixture of ethyl acetate-hexane (1:1, 2×50 mL). The organic phases were combined, dried with magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by silica gel chromatography eluting with a mixture of hexane-ethyl acetate (15:1), to give 4-(butyltelluro)butan-2-ol (2); yield: 0.89 g, (70%).
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- 14. Typical procedure for the preparation of the 1,4-dianion 4 and its reaction with aldehydes and ketones: To a round bottomed flask containing the hydroxytelluride 2 (0.25 g, 1 mmol) in THF (5 mL) at -70 °C under stirring, *n*-butyllithium (1.57 mL, 2.2 mmol from 1.4 mol/L solution

in hexanes) was added dropwise. The solution was stirred at the same temperature for 20 min and benzaldehyde (0.053 g, 0.5 mmol) was added. The reaction solution was warmed to 0 °C and a saturated solution of NH₄Cl (1 mL) was added. The mixture was transferred to a separatory funnel and the aqueous phase was extracted with ethyl acetate $(3 \times 5 \text{ mL})$. The organic phases were combined, washed with a diluted sodium hypochlorite solution, dried with magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by silica gel chromatography eluting with cyclohexane then with a gradient of ethyl acetate-cyclohexane (2:1), to give 6b, 1-phenylpentane-1,4-diol (CAS. 38299-94-4), as a diastereomeric mixture; yield: 0.08 g, (89%); ¹H NMR: (200 MHz, CDCl₃, ppm) δ 1.12 (d, J = 6.3 Hz, 3H); 1.13 (d, J = 6.3 Hz, 3H); 1.39-1.58 (m, 2H); 1.75-1.85 (m, 2H);3.70-3.83 (m, 1H); 4.61 (t, J = 5.1 Hz 1H); 4.66 (t, J = 6.0 Hz, 1H); 7.21–7.32 (m, 5H); ¹³C NMR: (50 MHz, CDCl₃, ppm) δ 23.2; 23.5; 34.7; 34.9; 35.9; 36.1; 67.6; 68.1; 73.9; 74.5; 125.7; 125.8; 127.2; 127.3; 128.3; 144.6; 144.8; LRMS *m*/*z* (rel. int.) 180 (M⁺, 20); 162 (35); 161 (44); 147 (22); 129 (16); 121 (21); 120 (77); 118 (31); 117 (53); 115 (15); 106 (100); 105 (63); 104 (30); 80 (20); 79 (80); 78 (47); 77 (70); 65 (11); 57 (17); 56 (59); 51 (47).

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- 16. Typical procedure for the cyclization of diols to the corresponding tetrahydrofurans: to a round bottomed flask containing the diol 6b (1 mmol, 0.18 g) in dichloromethane (3 mL) was added p-TSA (10 mg). The solution was refluxed for 12 h then diluted with a mixture of hexane-ethyl acetate (5 mL, 1:1) and washed with brine $(2 \times 3 \text{ mL})$. The organic phase was dried with magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by silica gel chromatography eluting with cyclohexane-ethyl acetate (30:1), to give 7b, tetrahydro-2-methyl-5-phenylfuran (CAS. 4457-59-4), as a diastereomeric mixture; yield: 0.14 g, (89%); ¹H NMR: (300 MHz, CDCl₃, ppm) δ 1.33 $(d, J = 6.0 \text{ Hz}, 3\text{H}); 1.38 (d, J = 6.0 \text{ Hz}, 3\text{H}); 1.55-1.95 (m, J = 6.0 \text{ Hz}, 3\text{Hz}); 1.55-1.95 (m, J = 6.0 \text{ Hz}, 3\text{Hz}); 1.55-1.95 (m, J = 6.0 \text{ Hz}); 1.55-1.95 (m, J = 6.0 \text{ Hz}); 1.55-1.95 (m, J = 6.0 \text{ Hz}); 1.55-1.95 (m, J = 6.0 \text{ H$ 2H); 2.04-2.44 (m, 2H); 4.13-4.42 (m, 1H); 4.89 (t, *J* = 7.2 Hz 1H); 5.05 (dd, *J* = 8.4, 6.6 Hz, 1H); 7.23–7.39 (m, 5H); ¹³C NMR: (75 MHz, CDCl₃, ppm) δ 21.3; 21.5; 33.0; 34.2; 34.6; 35.6; 75.8; 75.9; 80.2; 80.9; 125.5; 125.8; 126.9; 127.0; 128.0; 128.2; 143.4; 143.9; LRMS m/z (rel. int.) 180 (M⁺, 20); 162 (35); 161 (44); 147 (22); 129 (16); 121 (21); 120 (77); 118 (31); 117 (53); 115 (15); 106 (100); 105 (63); 104 (30); 80 (20); 79 (80); 78 (47); 77 (70); 65 (11); 57 (17); 56 (59); 51 (47).