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The soft nucleophilicity of organotellurolates driving the S_N2-type lactone ring-opening reaction

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ABSTRACT

Lithium and magnesium organotellurolates were reacted with lactones producing the corresponding tellurocarboxylic acids. Treatment of the reaction mixture with lithium aluminum hydride allowed the isolation of the corresponding hydroxytellurides in a one-pot operation.

One of the most expressive characteristics of chalcogenolate anions is their soft nucleophilicity and low basicity.[1] The lithium, sodium, and magnesium chalcogenolates are able to undergo S_N2-type reactions in the presence of acidic functionalities, for example, alcohols,[2] allowing the incorporation of the chalcogen moiety into organic substrates. This property of the metal chalcogenolates associated with their peculiar reactivity has been explored in the preparation of multi-functionalized chalcogen compounds, which can be submitted to further transformations based on the rich chalcogen chemistry.[3,4]

For many years we have been devoting our attention to the chemistry of organotellurides,[5] and more recently we became especially interested in applying these compounds as starting materials for natural product synthesis, exploring their inherent chemical properties.[6]

Organotellurium entities present a dual reactivity, that is, in metal organotellurolates the tellurium atom behaves as a soft nucleophile and in diorganotellurides it is attacked by nucleophiles, especially organolithiums, generating a new anionic center at the carbon atom where the tellurium atom was originally attached. This concept has been applied by us in the preparation of functionalized organolithium reagents by Te/Li exchange, and other organometallics by further transmetallation of the originally obtained organolithiums.[5,6] These organometallics have been used in the synthesis of bioactive compounds.[6,7]

In this work, taking advantage of the high soft character of the metal organotellurolates, we performed S_N2-type lactone ring-opening reactions by lithium organotellurolates,[8] aiming to obtain multifunctional building blocks with potential application in organic synthesis.

The most practical method to prepare metal tellurolates, which has been extensively employed by us in recent years, is the direct reaction of an organolithium or Grignard reagent with elemental tellurium in THF at room temperature, so avoiding the manipulation of bad-smelling alkaneditellurides.[8]

Reaction of metal organotellurolates with lactones in THF under reflux gave the corresponding tellurocarboxylic acids.[9] Treatment of the reaction mixture with lithium aluminum hydride led to the corresponding hydroxytellurides in a one-pot operation[10] (Scheme 1).

Initially, screening was carried out looking for the best nucleophilic tellurium species for the lactone ring opening of the γ-butyrolactone **1a** (Table 1).

As can be seen in Table 1, *n*-butyltellurol, the supposed nucleophilic tellurium species resulting of the reaction of lithium *n*-butyltellurolate with a proton source, failed to react with lactone **1a** even at long reaction times under reflux (Table 1, entries 1–3). Sodium *n*-butyltellurolate generated in situ by reacting the bad-smelling *n*-dibutylditelluride with sodium borohydride in THF gave the desired product in 42% isolated yield (Table 1, entry 4). Two equivalents of sodium *n*-butyltellurolate increased the yield, but not satisfactorily (Table 1, entry 5). On the other hand, when lithium *n*-butyltellurolate, prepared from elemental tellurium and *n*-butyllithium in THF, was reacted with **1a**, compound **4a** was isolated in 80% yield after 9 h under reflux (Table 1, entry 6). Use of 1.5 and 2.0 equiv of the nucleophile did not improve significantly the product yield (Table 1, entries 7 and 8). The magnesium

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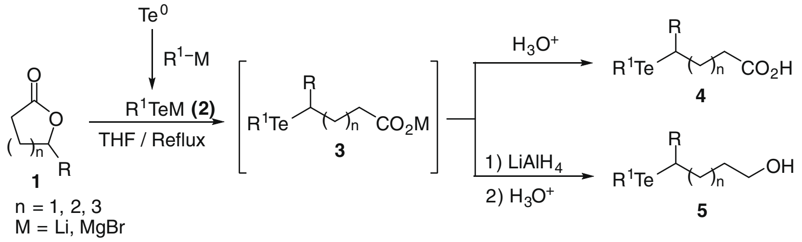
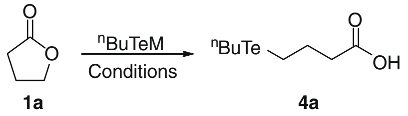


Scheme 1. Lactone ring opening by metal organotellurolates and reduction of the obtained carboxylate to the corresponding alcohol.

Table 1
Influence of the metal butyltellurolate in the ring-opening reaction of the γ-butyrolactone **1a**



Entry	^{n}BuTeM (equiv)	Conditions[c]	t (h)	Yield of **4a** (%)
1	^{n}BuTeLi (1.0)[a]	THF/H_2O	24	–
2	^{n}BuTeLi (1.0)[a]	THF/EtOH	24	–
3	(^{n}BuTe)$_2$ (0.5)[a]	EtOH/$NaBH_4$	24	–
4	(^{n}BuTe)$_2$ (0.5)	THF/$NaBH_4$	12	42
5	(^{n}BuTe)$_2$ (1.0)	THF/$NaBH_4$	12	55
6	^{n}BuTeLi (1.0)[a]	THF	9	80
7	^{n}BuTeLi (1.5)[a]	THF	9	86
8	^{n}BuTeLi (2.0)[a]	THF	8	88
9	^{n}BuTeMgBr (1.5)[b]	THF	10	82

[a] Generated by reacting elemental tellurium with *n*-butyllithium.
[b] Generated by reacting elemental tellurium with *n*-butylmagnesium bromide.
[c] Reactions performed at room temperature gave **4a** in low yields.

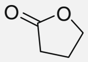
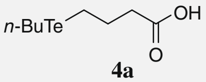
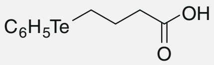
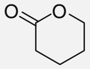
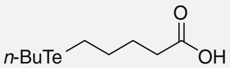
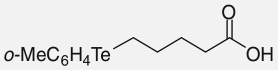
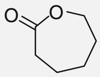
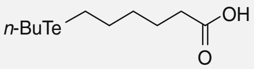
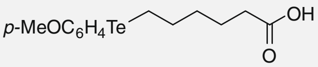
n-butyltellurolate presented reactivity similar to that of the lithium analog (Table 1, entry 9).

Use of HMPA or 18-crow-6 ether did not improve the yields. With these results in hands the best reaction conditions were applied to other lactones and metal organotellurolates. Table 2 summarizes the results obtained.

Lithium and magnesium organotellurolates reacted with five, six, and seven-member ring lactones in moderate to good yields (Table 2, entries 1–8). Some 4-substituted five-member ring lactones (Table 2, entries 7–10) were also reacted with metal organotellurolates. Albeit lactone **1d** underwent reaction with both lithium and magnesium tellurolates in good yields (Table 2, entries 7 and 8), the more sterically hindered homologous **1e** and **1f** failed to react in the same conditions (Table 2, entries 9 and 10).

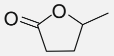
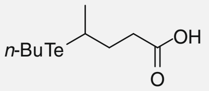
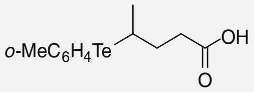
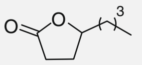
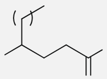
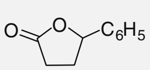
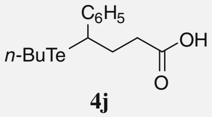
As mentioned before, we are interested in developing functionalized tellurides aiming their use in the synthesis of biologically active compounds. In this context, we developed extensive studies on the preparation of C,O-dianions from hydroxytellurides.[6,7] As an exten-

Table 2
Tellurocarboxylic acids prepared by lactone ring opening

Entry	RTeM (reaction time, h)	Lactone	Product	Yield[a] (%)
1	^{n}BuTeLi (**2a**) (9)	 **1a**	 **4a**	86
2	C_6H_5TeMgBr (**2b**) (10)		 **4b**	78
3	**2a** (8)	 **1b**	 **4c**	88
4	*o*-Me-C_6H_4TeMgBr (**2c**) (10)		 **4d**	77
5	**2a** (12)	 **1c**	 **4e**	60
6	*p*-MeO-C_6H_4TeMgBr (**2d**) (12)		 **4f**	68

(continued on next page)

Table 2 (*continued*)

Entry	RTeM (reaction time, h)	Lactone	Product	Yield[a] (%)
7	**2a** (10)	 **1d**	 **4g**	80
8	**2c** (11)		 **4h**	68
9	**2a** (24)	 **1e**	 **41**	–
10	**2a** (24)	 **1f**	 **4j**	–

[a] Isolated yields.

sion of these studies it would be interesting to transform the organyl tellurocarboxylic acids **2** into hydroxytellurides **5** (Table 3).

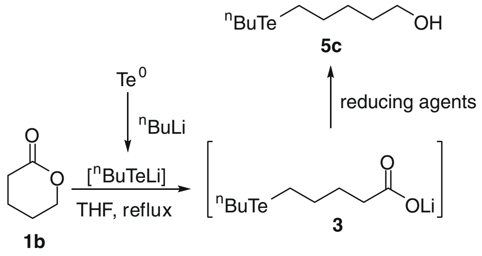
To this end, initially several reducing agents were tested to transform **3** into **5c**, as shown in Table 3.

Stoichiometric or excess amounts of sodium borohydride under reflux gave the hydroxyl telluride **5c** in only modest yields (Table 3, entries 1 and 2). Under similar conditions the use of DIBAL-H led to the desired product in better yields (Table 3, entries 3 and 4). However lithium aluminum hydride gave the best results (Table 3, entries 5–7) allowing the preparation of **5c** in a one-pot process in 75% yield when 0.8 equiv of $LiAlH_4$ was used. When higher amounts of $LiAlH_4$ were used lower yields were obtained (Table 3, entries 5 and 6).

The conditions employed for entry **7** (Table 3) were applied in the preparation of hydroxytellurides **5a**–**5e** as presented in Table 4.

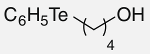
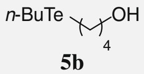
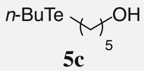
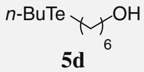
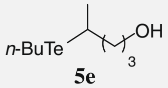
Only moderated yields were achieved in the reaction of lactones **1c** and **1d** with lithium *n*-butyltellurolate (Table 4, entries 4 and 5). By using phenyltelluro magnesium bromide as the nucleophile in the reaction with lactone **1a** compound **5a** was obtained in 65% isolated yield, after treating the reaction medium with $LiAlH_4$ (Table 4, entry 1). The carboxylate, produced by opening γ-valerolactone[1b] with **2a,** was reduced in situ to the corresponding alcohol **5c** in 75% isolated yield (Table 4, entry 3).

Table 3
One-pot reduction of carboxylates to the corresponding alcohols



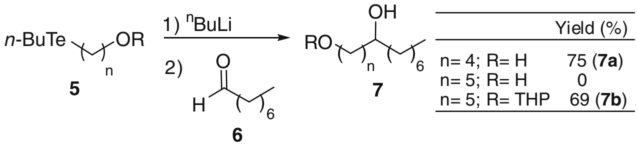
Entry	Reducing agent (equiv)	Reaction time (h)	Yield (%)
1	$NaBH_4$ (1.0)	12	30
2	$NaBH_4$ (1.5)	12	36
3	DIBAL-H (1.0)	5	52
4	DIBAL-H (1.5)	5	60
5	$LiAlH_4$ (1.0)	8	65
6	$LiAlH_4$ (1.5)	5	50
7	$LiAlH_4$ (0.8)	8	75

Table 4
Hydroxytellurides prepared

Entry	RTeM (reaction time, h)	Lactone	Product	Yield[a] (%)
1	**2b** (15)	**1a**	 **5a**	65
2	**2a** (15)	**1a**	 **5b**	72
3	**2a** (15)	**1b**	 **5c**	75
4	**2a** (20)	**1c**	 **5d**	50
5	**2a** (17)	**1d**	 **5e**	58

[a] Isolated yields.

As mentioned before, the Te/Li exchange reaction is one of the most synthetically useful reactions of the organotellurium compounds. In view of this fact, we submitted the prepared hydroxytellurides to the reaction conditions for this transformation. The hydroxytellurides **5b** and **5c** were treated with *n*-butyllithium in THF and then octanal (**6**) was added to the reaction mixture. In the case of compound **5b**, the diol **7a** was obtained in 75% yield. Under the same reaction conditions **5c** failed to react, being recovered unchanged on the work-up. When **5c** was transformed into the corresponding THP ether, the Te/Li exchange was successful, leading to compound **7b** in 69% yield on reaction with **6** (Scheme 2).



Scheme 2. Te/Li exchange reaction and capture of the corresponding organolithium with **6**.

Finally, it must be pointed out that all the organotellurides prepared in this work, except dibuylditelluride and dibutyltelluride, are not bad smelling and are stable to air and light.

In conclusion, a practical method to prepare organotellurocarboxylic acids in a single operation has been developed by using in situ-generated metal organotellurolates in a S$_N$2-type reaction with lactones. In addition, the intermediate organyl telluride carboxylates can be directly reduced to the corresponding hydroxyl tellurides, which are synthetic equivalents of the corresponding organolithiums by Te/Li exchange reaction.

Acknowledgments

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9. *Typical procedure for the lactone ring opening by lithium n-butyltellurolate.* 4-(*n*-butyltellanyl)butanoic acid (**4a**). To a dry two-necked 50 mL round-bottomed flask equipped with magnetic stirring, reflux condenser, and a rubber septum under nitrogen, was added elemental tellurium (0.51 g, 4.0 mmol) previously dried overnight in an oven at 100 °C. Then dry tetrahydrofuran (15 mL) was added. To the stirred suspension was added *n*-butyllithium (2.9 mL, 1.4 M in hexane). The mixture was then heated to 80 °C and the lactone **1a** (0.22 g, 2.6 mmol) was added all at once. The reaction was monitored by gas chromatography. After 9 h at 80 °C the reaction medium was allowed to reach the room temperature and then it was diluted with AcOEt (20 mL) and washed with saturated solution of NH$_4$Cl (15 mL). The phases were separated and the aqueous phase was extracted with AcOEt (2 × 20 mL). The organic phase was dried over MgSO$_4$ and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography eluting first with hexane to remove dibutylditelluride and then with hexane/AcOEt (8:2) to remove the product. Yield: 0.61 g (86%). ^{1}H NMR: (300 MHz, CDCl$_3$, ppm) δ 10.79 (br s, 1H); 2.66 (t, J = 7.5 Hz, 2H); 2.65 (t, J = 7.5 Hz, 2H); 2.48 (t, J = 7.2 Hz, 2H); 2.06 (quint., J = 7.5 Hz, 2H); 1.73 (quint., J = 7.2 Hz, 2H); 1.38 (sext., J = 7.5 Hz, 2H); 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ 179.43; 36.10; 34.28; 27.12; 25.07; 13.41; 2.83; 1.10. LRMS *m/z* (rel. int.) 274 (M$^+$, 15); 87 (100); 57 (54); 41 (70). IR $\nu_{\max}$ (neat) 3053, 2957, 1646, 1370.
10. *Typical procedure for the reduction of the organotelluro carboxylic acids.* 4-(Phenyltellanyl)but-1-ol (**5a**) (one-pot procedure). To a dry two-necked 50 mL round-bottomed flask equipped with magnetic stirring, reflux condenser, and a rubber septum under nitrogen, was added elemental tellurium (0.51 g, 4.0 mmol) previously dried overnight in an oven at 100 °C. Then dry tetrahydrofuran (15 mL) was added. To the stirred suspension was added phenylmagnesium bromide (2.9 mL, 1.4 M in hexane). The mixture was then heated to 80 °C and the lactone **1a** (0.22 g, 2.6 mmol) was dissolved in THF (5 mL) and added all at once. The reaction was monitored by gas chromatography. After heating at 80 °C for 10 h, LiAlH$_4$ (0.079 g, 2.1 mmol) was added in small portions. After 5 h at 80 °C the reaction mixture was allowed to reach the room temperature and then it was diluted with AcOEt (30 mL), treated with NaOH (1 mL, 1 M), and filtered under vacuum. The organic phase was washed with saturated solution of NH$_4$Cl (15 mL). The phases were separated and the organic phase was washed with AcOEt (2 × 20 mL). The organic phase was dried with MgSO$_4$, filtered, and the solvent was evaporated. The residue was purified by column flash chromatography eluting first with hexane to remove diphenylditelluride and then with hexane/AcOEt (8:2) to remove the product. Yield: 0.47 g (65%). ^{1}H NMR: (300 MHz, CDCl$_3$, ppm) δ 7.71 (dd, J = 6.9 Hz and 1.2 Hz, 2H); 7.16–7.29 (m, 3H); 3.61 (t, J = 6.3 Hz, 2H); 2.91 (t, J = 7.5 Hz, 2H); 2.31 (br s, 1H); 1.87 (quint., J = 7.2 Hz, 2H); 1.63 (quint., J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ 138.31; 129.13; 127.53; 111.63; 62.03; 34.77; 28.08; 8.23. LRMS *m/z* (rel. int.) 280 (M$^+$, 18); 73 (96); 55 (100); 43 (48). IR $\nu_{\max}$ (neat) 3372, 2930, 1059, 732, 691.