Tetrahedron Letters 50 (2009) 6368–6371

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Functionalized organozincates and organocuprates derived from γ-hydroxytellurides in the preparation of 1,4-hydroxyketones

Jefferson L. Princival, Alcindo A. Dos Santos *, João V. Comasseto

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, Cx.P. 26077, 05508-900 São Paulo, Brazil

ARTICLE INFO

Article history:
Received 31 July 2009
Revised 25 August 2009
Accepted 26 August 2009
Available online 1 September 2009

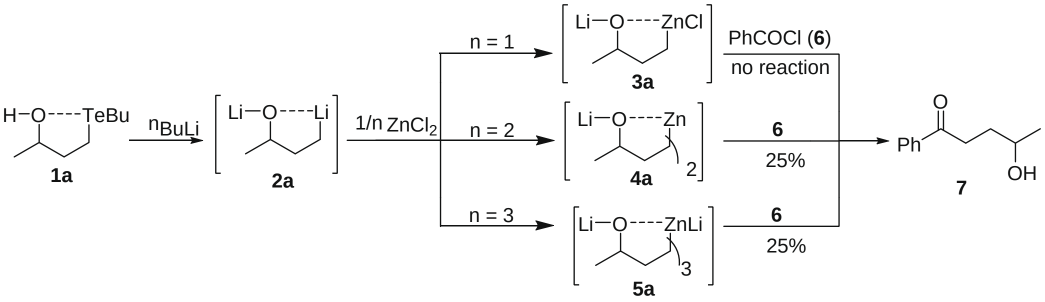
Keywords:
Hydroxyltellurides
Organozincates
Organocuprates
1,4-Hydroxyketones

ABSTRACT

A C–O-dianionic zincate was generated by a Te/Li exchange reaction of an alkyltelluride, followed by Li/Zn transmetallation and reaction with methyllithium. The reaction between the enantiomerically pure (99% ee) (*R*)-dianionic zincate and benzoyl chloride led to 3-hydroxy-1-phenyl pentanone with total retention of the carbon configuration (99% ee). Similar results were obtained using the corresponding Lipshutz cyanocuprates.

Functionalized non-stabilized organometallics are useful intermediates for the construction of multifunctional organic structures.[1] Among the most employed functionalized sp^3-hybridized organometallics for this end are the organozinc compounds.[2] The preparation of these species from organolithium reagents by transmetallation is a common practice.[1] The functionalized sp^3-hybridized organolithium precursors have been prepared by halogen-,[1b–d,h,i] sulfur–,[3] tin–[1b,4] and more recently, tellurium–lithium[5] exchange reactions. In this last case the progress has been slower, presumably due to the lack of reliable information on the physical and chemical characteristics of organotellurium compounds. Recent studies of our group showed that functionalized alkyltellurides are easily prepared and handled,[6] demonstrating stability to air and light, and exhibiting no bad smell, contrary to what is frequently reported about organotellurium compounds. Keeping these facts in mind, and considering the easy access to functionalized alkyltellurides in enantiomerically pure form,[6a,b,7] we report in this Letter a study on their transformation into 4-hydroxyketones, through the intermediacy of organozinc compounds. The fast tellurium/lithium exchange[5] and the inertness of both the starting alkyltelluride and the by-product dibutyltelluride toward the newly formed sp^3-hybridized organometallics are appealing features of our method to access these reactive intermediates.

The starting hydroxytelluride **1a** used in this study was prepared in 85% yield by hydrotelluration of methyl vinyl ketone, followed by carbonyl reduction with sodium borohydride.[6c,d,f]



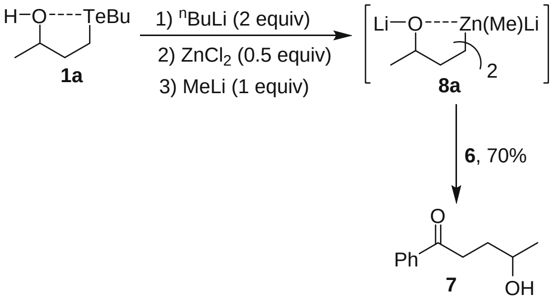
Scheme 1. Presumed structures of the organozinc species formed and their reaction with benzoyl chloride (**6**).

---

* Corresponding author. Tel.: +55 11 3091 2165; fax: +55 11 3815 5579.
E-mail address: alcindo@iq.usp.br (A. A. Dos Santos).

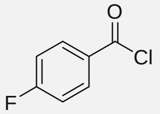
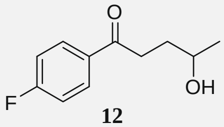
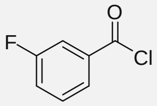
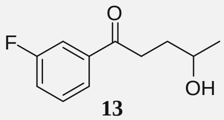
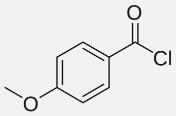
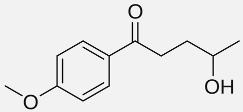
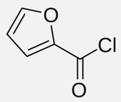
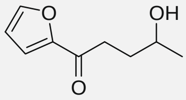
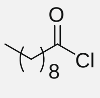
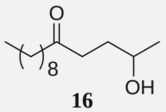
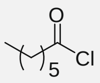
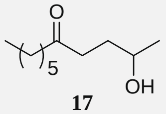
doi:10.1016/j.tetlet.2009.08.097

Compound **1a** is a yellow oil stable in air and ceiling light, and presents no bad smell. Enzymatic kinetic resolution of (***R,S***)-**1a** gave (***S***)-**1a** in 99% ee[7] The transformation of **1a** into the corresponding alkoxy-alkyllithium **2a** was performed by adding 2.0 equiv of *n*-buthyllithium to **1a** in THF at −78 °C. In a previous work, **2a** was captured with carbonyl compounds leading to the corresponding 1,4-diols.[6f]



Scheme 2. Reaction of the mixed hetero organozincate **8a** with **6**.

Table 1
Hydroxyketones prepared starting from hydroxytelluride **1a**

Entry	Substrate	Product[a]	Yield[b] (%)
1		 **12**	62
2		 **13**	67
3		 **14**	66
4		 **15**	58
5		 **16**	72
6		 **17**	72

[a] All compounds prepared showed analytical data compatible with the proposed structures.

[b] Isolated yields after column chromatography.

In this Letter, 1.0 equiv of the dianion **2a** was reacted with 1.0, 0.5, and 0.33 equiv of $ZnCl_2$ with the aim of preparing the corresponding mono-, di-, and tri-organozinc species. The resulting organometallic solutions were reacted with benzoyl chloride (**6**). The results are shown in Scheme 1.

The intermediate **3a** did not react with **6**, presumably due to the intramolecular stabilization of the O–Zn–C chelate with a high covalent bond character. Intermediates **4a** and **5a** reacted with **6** only in poor yields.

In view of the reactivity presented by entities **3a**–**5a**, and based on the works[8] concerning the enhancement of the reactivity of organozinc reagents, we decided to transform the intermediate **4a** into the corresponding heterozincate **8a** (Scheme 2). For this end telluride **1a** was reacted with 2 equiv of *n*-butyllithium, followed by 0.5 equiv of $ZnCl_2$ and then with 1.0 equiv of methyllithium. The heterozincate **8a** was reacted with benzoyl chloride (**6**) and the desired product **7** was obtained in 70% isolated yield.[9]

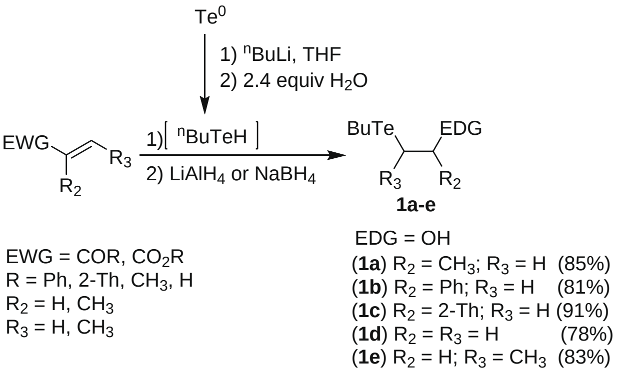
By using an enantioenriched sample of (***S***)-**1a** (99% ee),[7] the corresponding enantiomerically enriched zincate **8a** was obtained, which on reaction with benzoyl chloride (**6**) gave (***S***)-**7** with 99% ee.

With these results in hands, we reacted other acyl chlorides with the heterozincate **8a**, and several 3-hydroxyketones were produced in reasonable to good yields as presented in Table 1. Compounds **7**, **12–14** are analogous to Ipomeanol, a potent lung anticancer agent.[10]

In a previous work,[6c] we observed that the dianion **2a** can be transformed into the corresponding Lipshutz cuprate **3b** which reacts with 2-cycloexen-1-one as expected. This same cuprate reacted with benzoyl chloride (**6**) leading to **7** in 65% yield[11] (Scheme 3).

The generality of the above-commented transformations was demonstrated by preparing a number of different hydroxytellurides, as shown in Scheme 4, following a protocol similar to the one used to prepare **1a**.[6f]

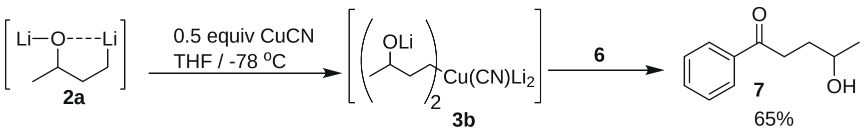
The hydroxytellurides **1a–e** prepared were submitted to the Te/Li exchange reaction and the corresponding lithium dianions were used in the formation of cuprates and zincates, as described above for **1a**. The zincates and cuprates derived from **1a–e** were reacted



EWG = COR, CO_2R
R = Ph, 2-Th, CH_3, H
R_2 = H, CH_3
R_3 = H, CH_3

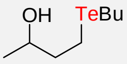
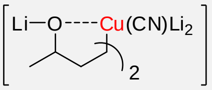
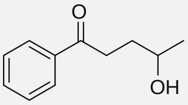
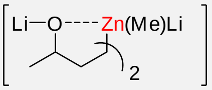
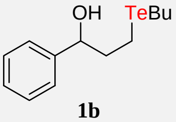
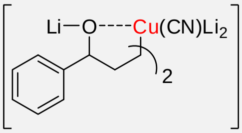
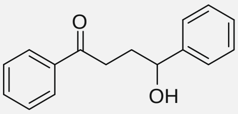
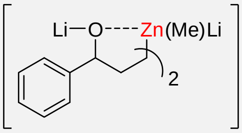
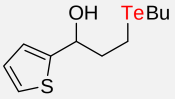
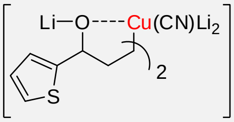
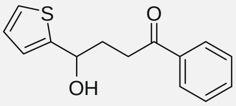
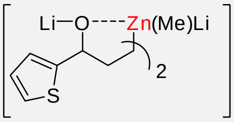
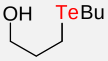
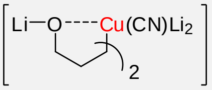
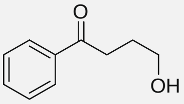
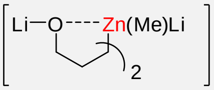
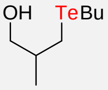
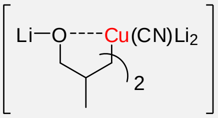
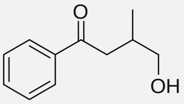
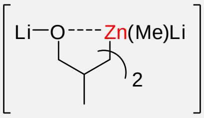
EDG = OH
(**1a**) $R_2 = CH_3$; R_3 = H (85%)
(**1b**) R_2 = Ph; R_3 = H (81%)
(**1c**) R_2 = 2-Th; R_3 = H (91%)
(**1d**) $R_2 = R_3$ = H (78%)
(**1e**) R_2 = H; $R_3 = CH_3$ (83%)

Scheme 4. Preparation of hydroxytellurides **1a–e**.



Scheme 3. Transformation of **2** into a Lipshutz cyanocuprate and its reaction with **6**.

Table 2
Hydroxyketones prepared starting from hydroxytellurides **1a–e**

Entry	Hydroxytelluride	Dianion	Product[a]	Yield[b] (%)
1	 **1a**		 **7**	65
2	**1a**		**7**	70
3	 **1b**		 **18**	77
4	**1b**		**18**	68
5	 **1c**		 **19**	73
6	**1c**		**19**	65
7	 **1d**		 **20**	67
8	**1d**		**20**	62
9	 **1e**		 **21**	63
10	**1e**		**21**	75

[a] All compounds prepared showed analytical data compatible with the proposed structures.
[b] Isolated yields after column chromatography.

with benzoyl chloride (**6**) giving the corresponding 4-hydroxyketones shown in Table 2.

Finally, it must be pointed out that all the organotellurium compounds described in this paper do not smell badly, and are stable in air and light.

In conclusion, hydroxyltellurides can be converted into organozincates and organocuprates by a Te/Li exchange reaction followed, respectively, by transmetallation with $ZnCl_2$ and reaction with CuCN. The zincates and cuprates react with acid chlorides giving 4-hydroxyketones.

Acknowledgments

The authors thank FAPESP, CNPq, and CAPES for financial support.

References and notes

1. (a) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583; (b) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139; (c) Maciá, B.; Gómez, C.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 6101; (d) Yus, M.; Torregrosa, R.; Pastor, I. M. *Molecules* **2004**, *9*, 330; (e) Calaza, M. I.; Yang, X.; Soorudram, D.;

Knochel, P. *Org. Lett.* **2004**, *6*, 529; (f) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333; (g) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215; (h) Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409; (i) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255; (j) Alonso, F.; Meléndez, J.; Yus, M. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 2628; (k) Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390; (l) Yong, K. H.; Lotoski, J. A.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 8248; (m) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.

2. (a) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107; (b) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017.
3. (a) Ahn, Y.; Cohen, T. *J. Org. Chem.* **1994**, *59*, 3142; (b) Liu, H.; Cohen, T. *J. Org. Chem.* **1995**, *60*, 2022.
4. (a) Klein, R.; Gowley, R. E. *J. Am. Chem. Soc.* **2007**, *129*, 4126. and references cited therein; (b) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213. and references cited therein.
5. (a) Petragnani, N.; Stefani, H. A. *Tetrahedron* **2005**, *61*, 1613; (b) Comasseto, J. V.; Barrientos-Astigarraga, R. E. *Aldrichim. Acta* **2000**, *33*, 66; (c) Reich, H. J.; Green, D. P.; Phillips, N. H.; Borst, J. P.; Reich, I. L. *Phosphorus Sulfur Silicon Relat. Elem.* **1992**, *67*, 83.
6. (a) Comasseto, J. V.; Gariani, R. A. *Tetrahedron* **2009**, *65*, 8447; (b) Bassora, B. K.; Da Costa, C. E.; Gariani, R. A.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron Lett.* **2007**, *48*, 1485; (c) Dos Santos, A. A.; Princival, J. L.; Comasseto, J. V.; Barros, S. M. G.; Brainer Neto, J. E. *Tetrahedron* **2007**, *63*, 5167; (d) Dos Santos, A. A.; Ferrarini, R. S.; Princival, J. L.; Comasseto, J. V. *Tetrahedron Lett.* **2006**, *47*, 8933; (e) Dos Santos, A. A.; Comasseto, J. V. *J. Braz. Chem. Soc.* **2005**, *16*, 511; (f) Princival, J. L.; Barros, S. M. G.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron Lett.* **2005**, *46*, 4423.
7. Dos Santos, A. A.; Da Costa, C. E.; Princival, J. L.; Comasseto, J. V. *Tetrahedron: Asymmetry* **2006**, *17*, 2252.
8. (a) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kakihara, Y.; Miyoshik, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 472; (b) Uchiyama, M.; Nakamura, S.; Ohwada, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 10897; (c) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934.
9. *General procedure for the hetero zincate **8a** preparation/capture*: *(S)-4-Hydroxy-1-phenylpentan-1-one* (**7**): A solution of the (***S***)-(**1a**) (520 mg, 2 mmol) in THF (10 mL) was cooled to −78 °C and *n*-butyllithium (1.74 mL, 4 mmol, 2.3 mol L^{-1}) was added. After 5 min freshly prepared THF solution of $ZnCl_2$ (1 mL, 1 mmol, 1 mol L^{-1}) was added and the mixture was allowed to warm up to −10 °C. The mixture was re-cooled to −78 °C and methyllithium (1.0 mL, 1 mmol, 1 mol L^{-1}) was added. The mixture was allowed to warm up to 0 °C. Then freshly distilled benzoyl chloride (**6**) was added (1 equiv) and the reaction mixture was stirred for 2 h, poured into aqueous ammonium chloride solution (2 mL), extracted with ether, and the ether layer was washed with water, dried over $MgSO_4$, evaporated and the residue was purified by silica gel (230–400 mesh) chromatography using ethyl acetate/hexane (1:1) to afford 125 mg of **7**. Oil; yield (70%); CAS NR 27927-59-9. ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.24 (3H, d, *J* = 6.1 Hz), 1.77–2.03 (2H, m), 2.99 (1H, s), 3.12 (2H, t, *J* = 7.0 Hz), 3.89 (1H, sext, *J* = 6.1 Hz), 7.40–8.00 (5H, m). ^{13}C NMR (50 MHz; $CDCl_3$) δ 23.5; 32.9; 34.7; 67.1; 127.9; 128.4; 132.9; 136.6; 200.8. IR (film) cm^{-1} 3420, 3062, 2967, 2929, 1682, 1597, 1449, 1278, 1208, 1128, 1075, 743, 691. MS *m*/*z* (rel int.) 160 (60), 115 (68), 105 (100), 77 (65), 50 (60), 43 (36). $[\alpha]_D^{24}$ +12.8 (*c* 1.4, $CHCl_3$); 99% ee.
10. (a) Nunes, M. G.; Dasai, D.; Koehl, W.; Spratt, T. E.; Guengerich, F. P.; Amin, S. *Cancer Lett.* **1998**, *129*, 131; (b) Lakhanpal, S.; Donehowe, R. C.; Rowinsky, E. K. *Invest. New Drugs* **2001**, *19*, 69.
11. *General procedure for the cuprate preparation/capture*: *(R,S)-4-Hydroxy-1-phenylpentan-1-one* (**7**): A solution of the (*R,S*)-(**1a**) (520 mg, 2 mmol) in THF (10 mL) was cooled to −78 °C, and *n*-butyllithium (1.74 mL, 4 mmol, 2.3 mol L^{-1}) was added. After 5 min this solution was transferred via a cannula to a THF (5 mL) and CuCN (0,179 g, 2 mmol) suspension. The resulting suspension was stirred until a clear, light yellow solution was formed (1 h at −78 °C). This solution was then transferred via a cannula to another flask containing benzoyl chloride (0.28 g, 2 mmol) in THF (4 mL). The resulting mixture was stirred at −78 °C for 30 min, warmed to room temperature, and then diluted with ammonium hydroxide/ammonium chloride solution (10%, 5 mL) and diethyl ether (5 mL). The mixture was maintained under vigorous stirring for 30 min and the phases were separated. The organic phase was washed with brine (2 × 3 mL) and the aqueous phase was extracted with ethyl acetate (5 mL). The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The resulting residue was purified by CC over silica gel, eluting with ethyl acetate/hexane (1:1) giving 116 mg of **7** (65%) as an analytically pure material. The spectral data are identical to those of the compound obtained above.