



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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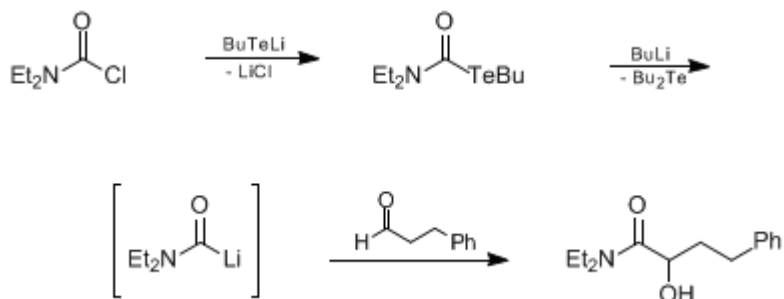
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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GENERATION OF N,N-DIETHYLCARBAMOYL LITHIUM VIA LITHIUM-TELLURIUM EXCHANGE AND ITS REACTION WITH 3-PHENYLPROPANAL: N,N-DIETHYL-2-HYDROXY-4-PHENYLBUTANAMIDE

[Benzenebutanamide, N,N-diethyl- α -hydroxy-]



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1. Procedure

Finely ground elemental tellurium (13.40 g, 105 mmol) (Note 1) and tetrahydrofuran (THF, 400 mL) (Note 2) are placed under nitrogen (N_2) in a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a N_2 inlet, 100-mL pressure-equalizing dropping funnel, and a rubber septum. Into the mixture is added ca. 65.5 mL (1.6 N in hexane, ca. 105 mmol) of butyllithium (Note 3) dropwise with a syringe through the septum with stirring at room temperature until the mixture becomes a pale yellow homogeneous solution (Note 4). The solution is stirred for 10 min, then cooled to -78°C . Diethylcarbamoyl chloride (12.7 mL, 13.56 g, 100 mmol) (Note 5) is injected through the septum with a syringe, and the solution is stirred at -78°C for 10 min. The cold bath is removed and the solution is allowed to warm to room temperature, then stirred for 1 hr. It is cooled again to -78°C , and 62.5 mL (1.6 N, 100 mmol) of butyllithium (Note 3) is injected over a 3-min period. After the solution is stirred at -78°C for 5 min, 13.42 g (100 mmol) of 3-phenylpropanal (Note 6) in 50 mL of THF is added from the dropping funnel over a 5-min period. The mixture is stirred for 10 min, warmed to room temperature, and stirred for 1 hr. The mixture is poured into 200 mL of a saturated ammonium chloride solution and extracted with diethyl ether (Et_2O) three times, 30 mL each. The combined organic layers are dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator at ca. 5 mm. The residual yellowish brown oil is chromatographed (silica gel, 50 mm \times 25 cm) (Note 7). The first, pale yellow fraction eluted with ca. 400 mL of hexane contains dibutyl telluride (23.62 g, 93% based on tellurium used) (Note 8). The next 500-mL fraction (eluted with hexane/ Et_2O , 10/1) contains by-products (Note 9). The desired product is eluted in the third fraction (ca. 500 mL of Et_2O) that is concentrated on a rotary evaporator and distilled to afford 19.35 g of N,N-diethyl-2-hydroxy-4-phenylbutanamide as a pale yellow viscous oil (bp $155\text{--}156^\circ\text{C}$ at 0.6 mm, 82%) (Note 10), (Note 11), (Note 12).

2. Notes

- The submitters used tellurium pieces from Aldrich Chemical Company, Inc., that were ground with a mortar and pestle just before use. The checkers found that direct use of tellurium powder (–60 mesh, Aldrich Chemical Company, Inc.) gave similar results.
- THF purchased from Wako Pure Chemical Industries, Ltd. (Japan) was used after distillation from Drynap. Drynap is a registered trademark of an alloy of sodium (above 8 wt%) and lead (90 wt%) produced by Dojin Chemical Research Center, Ltd. (Japan). Although Drynap is not essential and any

procedure can be used for drying THF provided that the THF is sufficiently dry for the usual reactions of organolithium compounds, the submitters often use this drying reagent when a large amount of solvent is needed since it is mild, much safer than sodium, and is easy to handle.

3. The submitters used butyllithium (1.6 M in hexane) from Nacalai Tesque Company, Ltd. (Japan). The checkers used butyllithium (1.6 M in hexane) from Aldrich Chemical Company, Inc.

4. The reaction is slightly exothermic. At this stage, lithium butanetelluroate (BuTeLi) is formed. (The checkers noted a deep red color as the BuLi was added.) BuTeLi should be prepared slightly in excess to the carbamoyl chloride. The subsequent step produces carbamoyllithium that may react with any excess carbamoyl chloride to give an undesired oxamide by-product.

5. The submitters used diethylcarbamoyl chloride from Aldrich Chemical Company, Inc., after fractional distillation. The checkers used the reagent without further purification with similar results.

6. The submitters used 3-phenylpropanal from Wako Pure Chemical Industries, Ltd., after distillation. The checkers used reagent obtained from Lancaster Synthesis without further purification with similar results.

7. The submitters used silica gel (mesh 100–200, BW-820 MH) from Fuji Davison Chemical, Ltd. (Japan). The checkers used radial chromatography (silica gel 60 PF 254 with gypsum, EM Science) with hexane/ethyl acetate (4/1) as eluent for small scale reactions. The checkers used flash chromatography (240 g of silica gel, grade 633, 47 × 61 microns, Davison Chemical) with hexane (1.5 L), hexane/ether (10/1, 1.5 L), and ether (1.5 L) as eluent for large scale reactions (100 mmol).

8. Elemental tellurium can be recovered from dibutyl telluride by the following procedure. Under nitrogen, naphthalene (4.0 g) and dry THF (100 mL) are placed in a flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a N₂ inlet, reflux condenser, and rubber septum. Sodium pieces (4.28 g, 186 mmol) are added to the solution slowly with stirring. After the solution turns deep blue, 4.50 g (18.6 mmol) of dibutyl telluride is added over a 3-min period with a syringe at room temperature. The rubber septum is replaced with a glass stopper and the mixture is refluxed for 2 days. The mixture is cooled to room temperature and ethanol is added very slowly until the sodium completely disappears. Air is bubbled into the solution with stirring for one day. The black solids that are obtained by filtration are washed well with Et₂O and dried (0.2 mm, 250°C, 4 hr) to give 2.22 g of elemental tellurium (93%, based on dibutyl telluride used). These conditions have not been optimized.

9. This fraction contains 3-phenylpropanal and 1-phenylheptan-3-ol that is formed by the addition of butyllithium to 3-phenylpropanal.

10. The physical properties are as follows: ¹H NMR (270 MHz, CDCl₃) δ: 1.09 (t, 3 H, J = 6.9), 1.10 (t, 3 H, J = 6.9), 1.72–1.94 (m, 2 H), 2.72–2.87 (m, 2 H), 2.98–3.13 (m, 2 H), 3.25 (dq, 1 H, J = 13.8, 6.9), 3.52 (dq, 1 H, J = 13.8, 6.9), 3.87 (d, 1 H, J = 7.8), 4.24 (ddd, 1 H, J = 7.8, 7.8, 2.9), 7.16–7.37 (m, 5 H); ¹³C NMR (68 MHz, CDCl₃) δ: 12.8, 14.0, 31.3, 37.4, 40.2, 40.8, 67.0, 120.0, 128.5, 128.6, 141.4, 173.6; IR (NaCl, neat) cm⁻¹: 3408, 1636. Anal. Calcd for C₁₄H₂₁NO₂: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.17; H, 9.08; N, 6.01.

11. Glassware is cleaned by soaking it overnight in a concd nitric acid bath.

12. When methyl benzoate was used as an electrophile instead of 3-phenylpropanal, N,N-diethylphenylglyoxylamide [Et₂NC(O)C(O)Ph] was obtained in a similar manner as a pale yellow viscous oil (bp 118–120°C at 0.2 mm, 13.40 g, 65 mmol, 65%), ¹H NMR (270 MHz, CDCl₃) δ: 1.15 (t, 3 H, J = 7.2), 1.29 (t, 3 H, J = 7.2), 3.24 (q, 2 H, J = 7.2), 3.56 (q, 2 H, J = 7.2), 7.50 (t, 2 H, J = 7.3), 7.63 (t, 1 H, J = 7.3), 7.94 (d, 2 H, J = 7.3); IR (NaCl, neat) cm⁻¹: 1681, 1636, 1448, 1232, 721.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

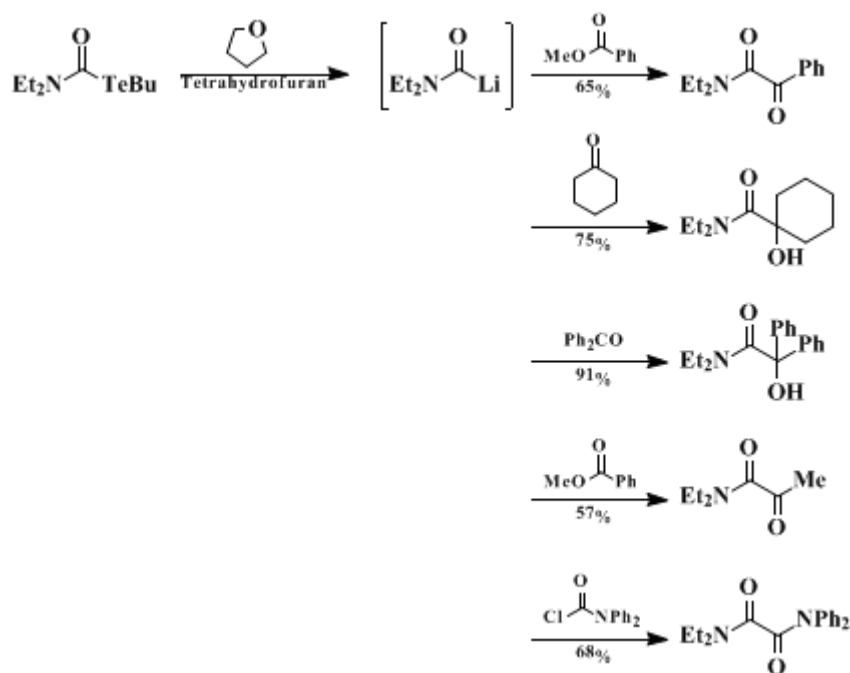
3. Discussion

Organic tellurium compounds react readily with organolithium reagents to give the thermodynamically more stable organolithium compounds via tellurium ate complexes. The lithium-tellurium exchange reaction proceeds quite rapidly at low temperatures, and can be used for the generation of a variety of organolithium compounds,^{2,3,4,5} including very reactive umpolung species, such as acyl-,³ aroyl-,³ and carbamoyllithiums.⁴ Among these, acyl- and aroyllithiums are kinetically very unstable, even at low temperatures, and dimerize quickly unless a suitable electrophile is present

when generated. In contrast N,N-dialkylcarbamoyllithiums are potentially useful synthetically since they are stable in THF at -78°C and can be efficiently trapped with various electrophiles.⁴

Carbamoyllithiums are attractive umpolung species that enable the straightforward introduction of carbamoyl moieties into organic molecules as nucleophiles. Although several methods have been reported for the generation of carbamoyllithiums, such as abstraction of the **formyl hydrogen**,⁶ insertion of **carbon monoxide** into lithium amides⁷ or lithium diaminocuprates,⁸ and transmetalation of a **biscarbamoylmercury**,⁹ these procedures have some disadvantages. Very few examples of **hydrogen** abstraction are reported, and satisfactory yields of the addition products are obtained only in the case of **N,N-diisopropylcarbamoyllithium**, or when the reaction is conducted in the presence of an electrophile. Reaction of **carbon monoxide** (CO) with lithium amides often gave complex results arising from the incorporation of two CO molecules. Diaminocuprates do not react satisfactorily with CO under atmospheric pressure.

The **lithium-tellurium** exchange reaction illustrated here provides a useful alternative to known methods. The reaction can be used to produce various α -hydroxyamides by using aldehydes and ketones as the electrophiles. Trapping the generated carbamoyllithium compounds with esters affords α -ketoamides in good yields (Scheme 1). α -Ketoamides with an aliphatic substituent on the carbonyl carbon cannot be obtained by palladium-catalyzed double carbonylation.¹⁰ Successful trapping of **N,N-diethylcarbamoyllithium** with **N,N-diphenylcarbamoyl chloride** to give an unsymmetrical oxamide demonstrates a synthetic use of carbamoyllithiums as the umpolung species of carbamoyl halides. A limitation of this procedure may arise from elimination of CO from the carbamoyllithiums. This becomes appreciable when a carbamoyl halide with an aromatic substituent on the **nitrogen** is used as a starting material. A variety of N,N-dialkylcarbamoyllithiums, such as N,N-diethyl-, N,N-dimethyl-, and N,N-pentamethylenecarbamoyllithiums can, however, be generated efficiently by the **lithium-tellurium** exchange reactions and trapped with various electrophiles to give the corresponding adducts in good yields.²



The present procedure provides a convenient method for the generation of carbamoyllithiums from carbamoyl halides and is very useful synthetically for the introduction of carbamoyl groups into organic molecules.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

silica gel

BuTeLi

Et₂O

[ethanol](#) (64-17-5)

[ethyl acetate](#) (141-78-6)

ether,
[diethyl ether](#) (60-29-7)

[ammonium chloride](#) (12125-02-9)

[hydrogen](#) (1333-74-0)

carbon monoxide,
[formyl hydrogen](#) (630-08-0)

[nitric acid](#) (7697-37-2)

[nitrogen](#) (7727-37-9)

sodium (13966-32-0)

Naphthalene (91-20-3)

methyl benzoate (93-58-3)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

3-phenylpropanal (104-53-0)

tellurium,
tellurium powder

N,N-Diethylcarbamoyllithium

LITHIUM-TELLURIUM

N,N-Diethyl-2-hydroxy-4-phenylbutanamide,
Benzenebutanamide, N,N-diethyl- α -hydroxy- (134970-54-0)

Diethylcarbamoyl chloride (88-10-8)

dibutyl telluride (38788-38-4)

Lithium butanetelluroate

1-phenylheptan-3-ol

N,N-diethylphenylglyoxylamide (34906-86-0)

biscarbamoylmercury

N,N-diisopropylcarbamoyllithium

N,N-diphenylcarbamoyl chloride (83-01-2)