Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A One-Pot and Efficient Preparation of (S)-Benzyl 4-Hydroxy-2-Pentynoate from (S)-n-Butyn-2-Ol Using an Unusual Lithiation with n-BuLi and a Catalytic Amount of Hexamethyldisilazane

Gaifa Lai [a] & Cesar Colon [a]
[a] Schering-Plough Research Institute, Chemical Process R & D , 1011 Morris Avenue, Union, New Jersey, 07083
Published online: 25 Sep 2007.

To cite this article: Gaifa Lai & Cesar Colon (1999) A One-Pot and Efficient Preparation of (S)-Benzyl 4-Hydroxy-2-Pentynoate from (S)-n-Butyn-2-Ol Using an Unusual Lithiation with n-BuLi and a Catalytic Amount of Hexamethyldisilazane, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:17, 3011-3016, DOI: 10.1080/00397919908086476

To link to this article: http://dx.doi.org/10.1080/00397919908086476

SYNTHETIC COMMUNICATIONS, 29(17), 3011-3016 (1999)

A ONE-POT AND EFFICIENT PREPARATION OF (*S*)-BENZYL 4-HYDROXY-2-PENTYNOATE FROM (*S*)-3-BUTYN-2-OL USING AN UNUSUAL LITHIATION WITH *n*-BuLi AND A CATALYTIC AMOUNT OF HEXAMETHYLDISILAZANE

Gaifa Lai*[1] and Cesar Colon

Schering-Plough Research Institute, Chemical Process R & D, 1011 Morris Avenue, Union, New Jersey 07083

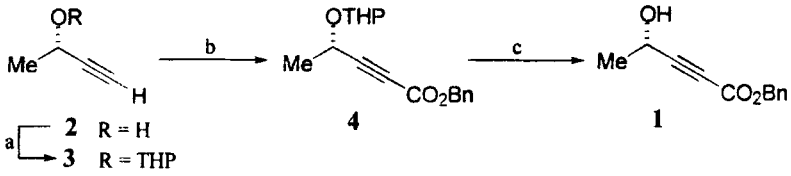
Abstract: A one-pot, four-step procedure was developed for the efficient preparation of (*S*)-benzyl 4-hydroxy-2-pentynoate (**1**) from (*S*)-3-butyn-2-ol (**2**), which involved as a key step the unusual lithiation of the silyl ether **5** with *n*-BuLi in the presence of a catalytic amount of hexamethyldisilazane (HMDS).

One-pot procedures for two or more sequential reactions are of great importance in organic synthesis both in laboratories and in industrial production.[2] In the course of our synthesis of himbacine analogues as potential therapeutical agents for Alzheimer's disease,[3] we required an efficient scalable preparation of (*S*)-benzyl 4-hydroxy-2-pentynoate (**1**), an early-stage key intermediate. One original synthesis of this intermediate, as depicted in Scheme 1, employed the tetrahydropyranyl (THP) ether as a hydroxyl-protecting group. However, preliminary work revealed that this route was not suitable for scale-up owing to several drawbacks, including low temperature (-78 °C) lithiation, tedious filtration of the resin in the deprotection step, and just moderate overall yield (50%). In this paper, we describe our investigation toward a new, one-pot, four-step procedure for the efficient preparation of the title intermediate **1** from (*S*)-3-butyn-2-ol (**2**)

* To whom correspondence should be addressed.

employing an unusual lithiation with *n*-BuLi and a catalytic amount of hexamethyldisilazane (HMDS) at enhanced temperatures (-30 to -25 °C).

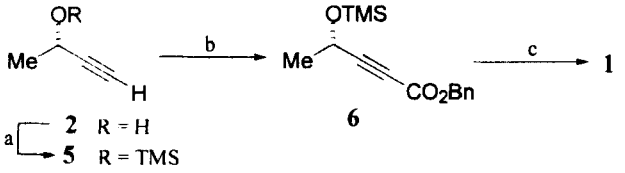
Scheme 1[a]



[a] Key: (a) dihydropyran, *p*-TsOH, THF, 0 °C to rt; (b) (i) *n*-BuLi, THF, -78 °C; (ii) $ClCO_2Bn$, -78 °C to rt; (c) DOWEX 50WX8-100 resin, MeOH, rt.

The starting enantiomerically pure (*S*)-3-butyn-2-ol (**2**) was obtained commercially [4] or by resolution[5] of its racemic mixture. The trimethylsilyl (TMS) ether was chosen as the protecting group in view of its facile introduction and removal under mild conditions.[6] Thus, the silylation of the alcohol **2** with 0.55 equiv of HMDS in THF at 68-70 °C for ca. 5 h cleanly afforded the silyl ether **5** in almost quantitative yield [7] with concomitant release of the byproduct, ammonia (Scheme 2). It was found that the mixture of solvent and **2** should be adjusted to pH 6-6.5 with sulfuric acid before addition of HMDS in order to facilitate this silylation.[8] When the reaction was complete, the mixture was just cooled down for direct use in next step.

Scheme 2[a]

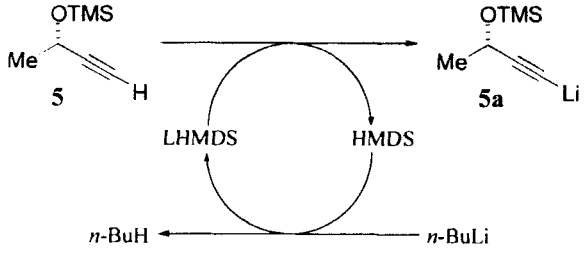


[a] Key: (a) HMDS (0.55 eq), THF, 68-70 °C; (b) (i) *n*-BuLi, HMDS (cat), -30 to -25 °C; (ii) $ClCO_2Bn$, -30 to -25 °C; (c) 6 N H_2SO_4.

The conversion of the silyl ether **5** to the benzyl ester **6** proceeded via a two-step sequence consisting of lithiation and carbobenzyloxylation. Treatment of **5** with *n*-BuLi even at low temperature (-78 °C), however, led to decomposition instead of the desired lithiation due to the incompatibility of the TMS group with this base. When LDA was used in the lithiation step, we detected a certain amount of the impurity benzyl *N,N*-diisopropylcarbamate [9] in the reaction mixture after carbobenzyloxylation. This carbamate apparently originated from reaction of the newly formed diisopropylamine with benzyl chloroformate. For large-scale reactions, this problem became more serious, up to 30-34% of the carbamate impurity, thus leading to a drastic decrease in yields.

With an attempt to inhibit such side reactions, we turned to assess the feasibility of lithium hexamethyldisilazide (LHMDS) as the lithiating agent because this is a more sterically hindered, less nucleophilic base than LDA.[10] As expected, lithiation of **5** with LHMDS,[11] followed by treatment with benzyl chloroformate, afforded significantly higher yields of the desired ester **6** without the corresponding carbamate impurity even at enhanced reaction temperatures (-30 to -25 °C). Furthermore, we gratifyingly found that *the use of n-BuLi in the presence of a catalytic amount of HMDS* (0.1 equiv) also ideally accomplished lithiation at the same temperatures and did not affect subsequent carbobenzyloxylation. This can be explained on the proposition that the ether **5** may be deprotonated to the lithium acetylide **5a** by LHMDS presumably generated *in situ* from *n*-BuLi and HMDS, as shown in Scheme 3. The two advantages of this new protocol are the less cost of reagents and the more convenient operation on a large scale. Finally, the removal of the TMS group in **6** was readily effected by direct treatment with 6 N H_2SO_4 solution, providing the title compound **1** in 72% overall yield starting from **2**.

Scheme 3



In conclusion, we developed a one-pot, four-step procedure for the efficient preparation of (*S*)-benzyl 4-hydroxy-2-pentynoate (**1**) from (*S*)-3-butyn-2-ol (**2**). This procedure featured an unusual lithiation using *n*-BuLi in the presence of a catalytic amount of HMDS at enhanced temperatures, much simpler operations, and higher overall yields, and thus can be applied to large-scale preparations.

Experimental Section

One-pot preparation of (*S*)-benzyl 4-hydroxy-2-pentynoate (1): A dry, 2-L, three-necked, round-bottomed flask, equipped with a thermometer, a mechanic stirrer, and a condenser, was charged with (*S*)-3-butyn-2-ol [4,5] (50 mL, 0.64 mol) and THF (200 mL). After the solution was carefully adjusted to pH 6-6.5 with concentrated H_2SO_4 solution, HMDS (74 mL, 0.35 mol, 0.55 equiv) was added in one portion. The mixture was agitated under nitrogen at 68-70 °C for ca. 5 h when ^{1}H NMR analysis showed that the silylation was complete.[7] The mixture was then cooled to rt, and another portion of HMDS (13.5 mL, 64 mmol, 0.1 equiv) was added. After the mixture was further cooled to -30 °C, *n*-BuLi (280 mL as a 2.5 M solution in hexanes, 0.7 mol, 1.1 equiv) was added dropwise with agitation over a period of 1 h, the temperature being maintained below -25 °C. After addition, the mixture was agitated at -30 to -25 °C for 30 min when ^{1}H NMR analysis indicated that the lithiation was almost complete.[11] To the resultant mixture was added a solution of benzyl chloroformate (100 mL, 0.7 mol, 1.1 equiv) in THF (100 mL) over a period of 1.5 h below -25 °C. After the mixture was agitated at -30 to 25 °C for 1 h, 6 N H_2SO_4 solution (300 mL, 0.9 mol) was added slowly below 10 °C, and the reaction mixture then allowed to agitate at rt for 2 h. The organic layer was separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (2 x 200 mL). The combined organic layers were washed in turn with brine, 5% NH_4OH solution, and water, dried over $MgSO_4$, filtered through a short silica gel column, and concentrated under reduced pressure to give 102 g (72% overall yield, 92% purity by HPLC [12]) of the title compound **1** as a pale brown oily liquid. An analytical pure sample was prepared by flash chromatography (silica gel, 230-400 mesh, EtOAc-hexanes, 1:5). Pure fractions were evaporated and dried under vacuum to give a pale yellow oily liquid: R_f 0.17 (EtOAc-hexanes, 1:5); HPLC R_t 7.17 min;[12] ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 5.21 (s, 2 H), 4.61 (q, J = 6.6

Hz, 1 H), 1.49 (d, J = 6.7 Hz, 3 H). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.71; H, 5.68.

Acknowledgment. The authors thank Dr. Xiaoyong Fu and Dr. Donal Maloney for helpful discussions on this work.

References and Notes

(1) Address for correspondence: 4 Marvin Lane, Piscataway, New Jersey 08854, USA.

(2) For an excellent recent example of one-pot transformations, see: Misner, J. W.; Kennedy, J. H.; Biggs, W. S. *Org. Proc. Res. Develop.* **1997**, *1*, 77.

(3) (a) Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 61. (b) Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812.

(4) (*S*)-3-Butyn-2-ol (**2**) was purchased from Aldrich Chemical Company.

(5) (*S*)-3-Butyn-2-ol (**2**) was also resolved from its racemic mixture via reaction with phthalic anhydride in *tert*-butyl methyl ether, followed by treatment with (*R*)-1-phenylethylamine.

(6) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, 2nd ed.; J. Wiley and Sons, Inc.: New York, 1991.

(7) We used ^{1}H NMR analysis to monitor the silylation. ^{1}H NMR ($CDCl_3$) for the silyl ether **5**: δ 4.28-4.23 (dq, J = 2.0, 6.5 Hz, 1 H), 2.23 (d, J = 2.1 Hz, 1 H), 1.16 (d, J = 6.6 Hz, 3 H), -0.08 (s, 9 H).

(8) We observed that the silylation was very slow when the mixture of solvent and alcohol **2** appeared neutral or slightly basic (pH 7-8).

(9) Benzyl *N*,*N*-diisopropylcarbamate was isolated as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 7.40-7.30 (m, 5 H), 5.15 (s, 2 H), 4.05 (low but very broad, 2 H), 1.23 (d, J = 6.8 Hz, 12 H).

(10) Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18.

(11) ^{1}H NMR sample was prepared by mixing 0.2 mL of the reaction mixture

and 0.5 mL of $CDCl_3$ and then adding two drops of 5% D_2SO_4 solution in D_2O. The disappearance of the doublet peak near 2.23 ppm on the spectrum indicated the complete lithiation of the silyl ether **5**.

(12) HPLC conditions: column, Symmetry C_{18} (3.9 mm x 150 mm, Waters); mobile phase, CH_3CN/H_2O (40:60); flow rate, 1.0 mL/min; detector, 230 nm; room temperature.

(Received in the USA 11 February 1999)