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Improved Large-Scale Synthesis of(*R*)-Benzyl 4-Hydroxyl-2-pentynoate from (*R*)-3-Butyn-2-ol

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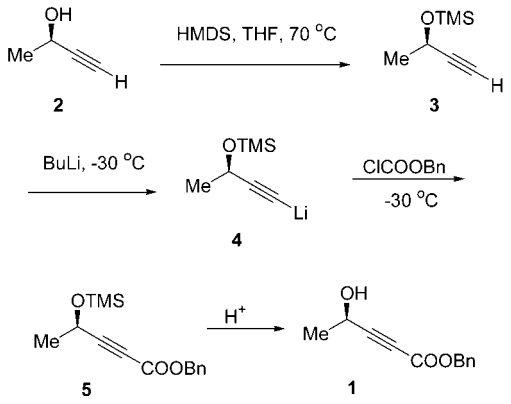
Abstract:
A reliable one-pot process for the title compound has been developed for large-scale productions. The effect of reaction conditions such as temperature, order of addition, and amount of the lithiation reagent has been extensively investigated, giving rise to an optimal process with highest attainable yield.

As a part of our drug development effort in synthesizing himbacine analogues, the potential therapeutical agents for Alzheimer's disease,[1,2] we needed to identify an efficient way to produce (*R*)-benzyl 4-hydroxyl-2-pentynoate **1** in multi-kilogram scale. A one-pot, four-step procedure from (*R*)-3-butyn-2-ol[3] as shown in Scheme 1 was reported. This procedure utilized trimethylsilyl (TMS) as the hydroxyl protection group that could be removed during aqueous work up. Lithiation of the TMS-protected butynol **3** in the presence of hexamethyldisilazane (HMDS) with *n*-butyllithium (n-BuLi), followed by the addition of benzyl chloroformate at −25 to −30 °C. Subsequent hydrolysis provided the desired product **1** in moderate yields after acidic workup.[4] However, this procedure was found to be not reproducible even on relatively small scale. Furthermore, an attempt to scale-up the process in the plant failed to produce any useful material, but rather a complex mixture containing only about 20% of the desired product **1**. This situation prompted us to undertake a more extensive study on the reaction. In this contribution we present a detailed study that resulted in a process with excellent yield on multikilogram-scale productions.

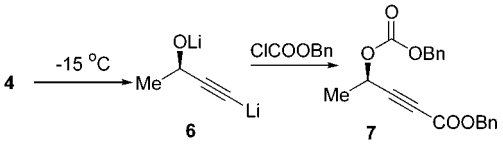
Scheme 1



Result and Discussion

Stability of Lithium Acetylide 4. It is important to determine the stability of lithium salt **4** at different temperatures. The lithiation reaction must be carried out below a temperature that does not result in decomposition of the acetylide **4**. One of major decomposition products appeared to be the cleavage of the TMS protecting group, leading to the formation of bis-lithium salt **6** as shown in Scheme 2. The mechanism for the formation of **6** is unknown, but presumably it occurs through an intermolecular exchange pathway. When the reaction mixture **6** was treated with benzyl chloroformate, bis-carbobenzylation product **7**[5] was detected as the major impurity in the final product. To determine the stability of **4**, a solution of **4** was generated at −30 °C and aged at different temperatures for 5 or 6 h before benzyl chloroformate treatment. As shown in entry 1 of Table 1, compound **4** showed very high stability at −25 °C. Upon the treatment of the aged solution with benzyl chloroformate, only a trace amount of impurity **7**[6] was observed in the final product. In contrast, experiments showed that decomposition of **4** became increasingly noticeable at elevated temperatures. A 5% and a significant 45% of the impurity was observed at −15 and 0 °C, respectively. These results suggested that **4** is stable in solution only at a temperature below −25 °C and therefore the lithiation must be done at below this critical temperature to avoid any decompositions.

Scheme 2



Effect of Order of Addition on Reaction Yield. When benzyl chloroformate was added to the solution of compound **4** (normal addition), the resulting intermediate **5** was partially decomposed to some unidentified impurities during the course of addition, presumably through nucleophilic attack of the acetylide **4** on the ester group of **5**. To avoid this

(1) Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; Mckinney, M. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 61.
(2) Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc*. **1996**, *118*, 9812.
(3) (*R*)-3-Butyn-2-ol was resolved from its racemic mixture via reaction with phthalic anhydride, followed by treatment with (*R*)-1-phenylethylamine. The product was isolated as a THF solution. The concentration was determined by GC analysis.
(4) Lai, G.; Colon, C. *Synth. Commun*. **1999**, *29*, 3011. The configuration of the starting material **2** and the product **1** was described as (*S*) in this paper, despite the fact that the (*R*) isomer was the development candidate.
(5) An analytically pure sample was isolated by preparative TLC (silica gel, ethyl acetate/hexane, 30/70). ^{1}H NMR ($CDCl_3$) δ 7.40 (br, 10 H), 5.45 (q, 1H), 5.30 (s, 2H), 5.25 (s, 2H), 1.60 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 152.8, 151.7, 133.6, 133.5, 127.70, 127.68, 127.64, 127.61, 127.40, 124.8, 83.4, 69.2, 66.9, 62.4, 28.7, 19.3.
(6) The content of impurity **7** was determined by ^{1}H NMR analysis based on the integral ratio of signals at 5.45 (q, 1H) for **7** and 4.65 (q, 1H) for **1**.

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Table 1. **Stability of 4**

entry	*T* (°C)	time (h)	**7** (%)
1	−25	6	<1
2	−15	5	5
3	0	5	45

Table 2. **Effect of order of addition**

entry	order of addition	*T* (°C)	yield (%)
1	normal	−78	85
2	reverse	−78	88
3	normal	−30	32
4	reverse	−30	86

undesired side reaction, a reverse addition was performed by adding a solution of **4** to the solution of benzyl chloroformate. Since the concentration of lithium acetylide **4** remained very low in the reaction mixture and it reacted much faster with benzyl chloroformate than with **5**, a much cleaner reaction and significantly higher yield were achieved. As shown in Table 2, the effect of the addition order on the product yield was minimal at the low temperature (entries 1 and 2), but a striking difference was observed at the elevated temperature (entries 3 and 4). These results also suggested that under reverse-addition conditions, the reaction yield was much less sensitive to the reaction temperature. Better, the highly exothermic nature of the reaction made it very difficult to maintain the reaction at low temperature, and reverse addition appeared to be a practical solution when running large-scale productions.

Compatibility of BuLi and TMS Group. It has been previously reported[4] that the treatment of **3** with n-BuLi led to decomposition even at −78 °C due to the incompatibility of n-BuLi and the TMS protecting group; n-BuLi could only be used as the lithiation reagent when 0.1 equiv of HMDS was present. The explanation was that n-BuLi deprotonated HMDS to form lithium bis(trimethylsilyl)amide in situ that acted as a deprotonation reagent, converting **3** to **4**. Our experiments indicated that these statements were probably made on the basis of incomplete studies and that the observed decomposition might have been complicated by other factors such as overcharging of n-BuLi. Extensive experiments showed that there was no apparent compatibility issue between n-BuLi and the TMS group even if the lithiation was done at a considerably high temperature of −25 °C. It was not only unnecessary to add the extra 0.1 equiv of HMDS before the n-BuLi charge, but also a reaction from a solution of **3** in THF containing no HMDS or a trace amount of HMDS provided a slightly better yield of the final product **1** (85−89%).[7] Decomposition was observed only in experiments where an excess amount of n-BuLi was charged. In addition, it is generally unlikely that n-BuLi would deprotonate HMDS in preference to an acetylenic hydrogen since the acidity of an acetylene is much higher than an amine (pK_a of approximately 23 and 38, respectively).[8]

Table 3. **Effects of the amount of BuLi**

entry	BuLi (equiv)	**1** (1%)
1	0.97 to 0.99	85−90
2	0.87	75
3	1.12	64

Effects of Overcharge and Undercharge of BuLi. It is crucial to charge exactly or near exactly 1 equiv of n-BuLi to maximize the reaction yield. Due to the variable moisture level and accuracy of the concentration measured for both the starting material and n-BuLi solutions, addition of 1 equiv of n-BuLi by calculation often led to unsatisfactory results. To prevent an overcharge of n-BuLi, a preferable 0.80 equiv of n-BuLi was initially charged, and the extent of lithiation was monitored thereafter. Small increments of n-BuLi, if necessary, were charged until a near-complete lithiation was reached.[9] Implementation of an appropriate sampling technique also played a critical role in determining the lithiation progress. When the lithiation process was well controlled and the resulting solution was mixed with benzyl chloroformate by reverse addition, the yield for product **1** was typically between 85 and 90%, regardless of the reaction scale.[10] As shown in Table 3, on one hand an undercharge of n-BuLi led to a lower yield because of lower conversion, whereas on the other hand, an overcharge of n-BuLi could cause even more damage. Addition of excess n-BuLi clearly produced **7** as the major impurity through intermediate **6**, suggesting that n-BuLi attacked the TMS protecting group when acetylene **3** was not present.

Conclusions

The reaction conditions that can affect this one-pot process have been carefully examined and optimized. The study clarified the compatibility issues between n-BuLi and the TMS protecting group. The process has been scaled to produce multikilogram product **1** in the plant with excellent yield by employing the conditions presented in this report, and product **1** has been used without further purification for the synthesis of himbacine analogues.

Experimental Section

Benzyl chloroformate, racemic 3-butyn-2-ol, HMDS, and n-BuLi were purchased from Aldrich. NMR spectra were recorded on a Bruker 400 MHz spectrometer. HPLC analysis was performed on Waters 2690 Alliance using the following

(7) Compound **2** was converted to **3** quantitatively by refluxing an acidic solution of **2** in THF (pH ≈ 3) with slight excess of HMDS. The resulting solution contained small amounts of HMDS and ammonium salts as the impurities. Compound **3** could be isolated as a THF solution by distillation. The distillate contained either no HMDS or trace amount of HMDS. Both distilled or nondistilled solution could be used for the next step. However, controlled experiments showed that the reactions from distilled solutions consistently gave slightly better yield.

(8) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: 1992; p 252.

(9) Sampling must be done completely under nitrogen because of the highly hydroscopic nature of the reaction mixture. Our experiments showed that quenching the reaction mixture into CD_3COOD inside the reaction flask under nitrogen provided consistent results. The vial that contained CD_3COOD was brought into the flask by tweezers. A few drops of reaction mixture were withdrawn to a dry pipet and quenched into the NMR solvent immediately. Precautions should be taken to keep the reaction mixture only on the tip of the pipet. Inappropriate sampling often led to underestimating the extent of the lithiation and unsatisfied results. A similar sampling technique was successfully used in the plant

(10) For production in the plant, the THF solution of the acetylide was transferred to the reactor containing benzyl chloroformate solution through an insulated stainless steel tube (diameter 0.25 in.).

conditions: column, Symmetry C18 (3.9 mm × 150 mm, Waters); mobile phase, MeCN/H_2O (40:60); flow rate of 1.0 mL/min; and detector at UV 230 nm.

Preparation of 1. A solution containing 7.5 g (107 mmol) of (*R*)-3-butyn-2-ol was reacted with HMDS by using the procedure reported previously.[4] Compound **3** was then distilled out at 1 atm as a THF solution. Toluene (10 mL) was then added to the distillation flask, and the mixture was distilled out and mixed with the THF solution. The resulting solution was cooled to about −30 °C, and an n-BuLi solution in hexane (86 mmol, 0.80 equiv) was charged while maintaining the reaction temperature between −25 and −30 °C. The reaction was monitored by ^{1}H NMR,[9] and additional amounts of n-BuLi were charged based on NMR analysis. To analyze the extent of lithiation by ^{1}H NMR, a few drops of the reaction mixture were quenched into 1.0 mL of CD_3-COOD. The reaction was assessed on the basis of the integral ratio of the peaks at 2.2 ppm (doublet, the proton on acetylene carbon) to the peaks at 4.3 ppm (multiple, the proton on hydroxy carbon). A ratio of 0.2 to 1.0, for example, indicated that 20% of **3** was still present and an additional amount of BuLi (20% of the amount initially charged) should be added. The same sampling procedure was repeated until the deprotonated acetylene was greater than 97%. The solution was transferred slowly through a cannula to a solution of benzyl chloroformate (128 mmol, 1.2 equiv) in 50 mL of THF at −30 °C.[10] The reaction mixture was stirred for 30 min and quenched with 50 mL of 6 N H_2SO_4 solution. The mixture was stirred for 1 h at room temperature. Toluene (50 mL) was charged, and the organic phase was separated and treated with 5% ammonium hydroxide solution to destroy the excess benzyl chloroformate. The organic solution was washed with water and dried on Na_2SO_4. Solvent was removed under vacuum to give 30.6 g of red oil. The yield of **1** was determined by HPLC as 18.6 g, 86% yield. An analytical sample was isolated by preparative HPLC as pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 1H), 5.23 (s, 2H), 4.65 (q, 1H), 2.10 (br, 1H), 1.53 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 153.2, 134.6, 128.7, 128.6, 88.8, 75.6, 67.8, 58.0, 23.2.

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