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Synthesis of ω-Hydroxy Ketones from ω-Benzyloxy Weinreb Amides by Using a Chemoselective Nucleophilic Addition/Birch Reduction Process

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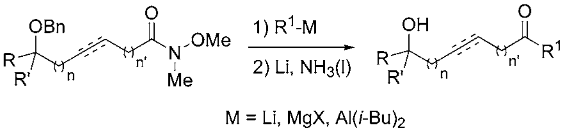
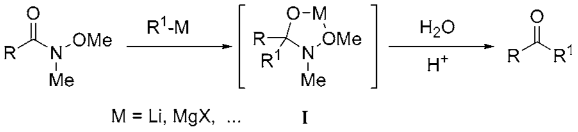
ABSTRACT



A chemoselective nucleophilic addition/Birch reduction process applied to ω-benzyloxy Weinreb amides led to ω-hydroxy ketones in good yields.

Weinreb amides have emerged as highly effective acylating agents for a wide range of nucleophiles.[1] Even with a large excess of the organometallic reagent, such amides lead to ketones exclusively due to the exceptional stability of the tetrahedral intermediate **I** (Scheme 1) that is generated in situ. No over addition occurs due to chelation of the metal ion between the resulting alkoxide and the oxygen atom of the *N*-methoxy group, which prevents premature release of the ketone functionality or formation of an iminium intermediate until an acidic work-up has been performed. This remarkable behavior of Weinreb amides allows them to be converted into aldehydes when treated with aluminum or boron hydrides.[1]

Scheme 1. Nucleophilic Addition to Weinreb Amides



The high stability of the tetrahedral intermediate **I** can also allow additional functionalization at other remote sites within a molecule.[2]

To avoid several protection−deprotection steps in multistep syntheses of highly functionalized compounds, efficient and chemoselective reactions have to be devised and/or latent protecting groups have to be found. Herein, we would like to report that intermediates of type **II** can serve as a latent carbonyl protecting group for the preparation of ω-hydroxy ketones from functionalized ω-hydroxy-protected Weinreb amides when a combined nucleophilic addition/Birch reduction process is used (Scheme 2).

Initially, the feasibility of the idea was investigated on the δ-benzyloxy Weinreb amide **1** using *n*-BuLi as a nucleophile. Addition of *n*-BuLi (5 equiv) in THF at −78 °C to compound **1** led to the lithiated tetrahedral intermediate of type **II**,[3] which was added to a solution of lithium in liquid

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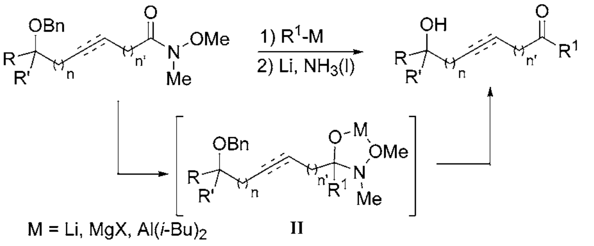
[1] (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) O'Neill, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 399−407. (c) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15−40. (d) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517−524. (e) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340−347.

[2] (a) Evans, D. E.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526. (b) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260−6268. (c) Evans, D. E.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613−7630. (d) Bergman, R.; Hansson, T.; Sterner, O.; Wickberg, B. *Chem. Commun.* **1990**, 865−867. (e) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317−6328.

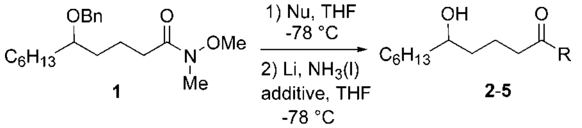
10.1021/ol049434f CCC: $27.50

Scheme 2. Nucleophilic Addition/Birch Reduction Process



ammonia [Li (excess), NH_3(l)] at −78 °C. After 5 min, the reaction was quenched with solid ammonium chloride and the hydroxy ketone **2** was isolated in 78% yield (Table 1, entry 1). The addition of *t*-BuOH (20 equiv) to the Li, NH_3(l) solution, which is usually recommended for efficient cleavage of benzyloxy groups,[4a] slightly improved the yield of hydroxy ketone **2**; this compound being isolated in 85% yield (Table 1, entry 2).

Table 1. Addition of Various Nucleophiles/Birch Reduction



1 → **2-5**

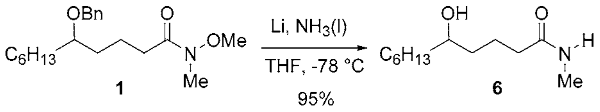
entry	nucleophile	additive	R	product	yield (%)
1	*n*-BuLi		Bu	**2**	78
2	*n*-BuLi	*t*-BuOH	Bu	**2**	85
3	EtMgBr	*t*-BuOH	Et	**3**	58[a]
4	AllyMgBr	*t*-BuOH	allyl	**4**	85[b]
5	(*i*-Bu)$_2$AlH	*t*-BuOH	H	**5**	70[c]

[a] Conversion of the starting amide **1** was completed by warming to 0 °C (alkylation step). [b] **4** partially cyclized to the corresponding lactols. [c] **5** cyclized to the corresponding lactols.

Likewise, the addition of ethylmagnesium bromide and allylmagnesium bromide to **1** led to magnesium intermediates of type **II**, which were added to Li, NH_3(l) solutions in the presence of *t*-BuOH to afford the corresponding δ-hydroxy ketones **3** (58% yield) and **4** (85% yield) respectively (Table 1, entries 3 and 4). Significantly, reaction of **1** with Dibal-H and the subsequent addition of the reaction mixture to a solution of Li, NH_3(l) in the presence of *t*-BuOH provided the δ-hydroxy aldehyde **5** as a diastereomeric mixture of lactols (2:1 ratio) in 70% yield (Table 1, entry 5).

It is worth noting that the selective debenzylation of **1** was also tested [Li, NH_3(l), −78 °C, 5 min]. However, only the secondary hydroxy amide **6** was isolated in 95% yield (Scheme 3). No selectivity was observed as the amide **1** underwent simultaneous *O*-debenzylation and *N*-demethoxylation, as previously reported for *N*-alkoxyamides.[4]

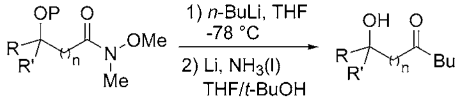
Scheme 3. Reactivity of Benzylated Weinreb Amide **1** under Birch Reduction Conditions



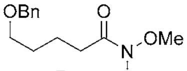
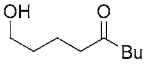
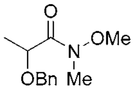
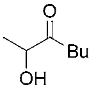
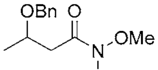
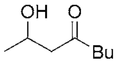
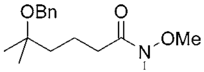
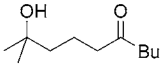
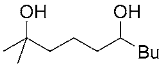
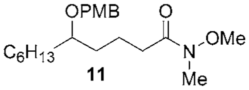
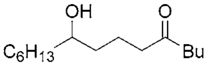
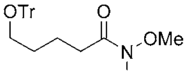
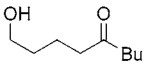
1 → **6**

To explore the scope of the nucleophilic addition/Birch reduction process, the influence of the substitution pattern present in the starting substrates was first examined. In a systematic study, only *n*-BuLi was used as a nucleophile. When the primary benzyloxy amide **7** was subjected to the nucleophilic addition/Birch reduction process under optimized conditions, the hydroxy ketone **13** was isolated in 72% yield (Table 2, entry 1). In addition to **1**, the secondary benzyloxy amides **8** and **9** were converted to the correspond-

Table 2. Consecutive Addition of Nucleophiles/Birch Reduction Process



n = 0, 3 **1, 7-12** → **13-17**

entry	amides	products (yield)
1	 **7**	 **13** (72%)
2	 **8**	 **14** (59%)
3	 **9**	 **15** (58%)
4	 **10**	 **16** (16%)  **17** (51%)
5[a]	**10**	**16** (92%)
6[b]	 **11**	 **2** (74%)
7[c]	 **12**	 **13** (70%)

[a] Debenzylation step carried out without *t*-BuOH. [b] PMB = *p*-MeO-C_6H_4-CH_2. [c] Tr = Ph_3C.

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(3) Complete conversion of the starting amide was ascertained by TLC after aqueous workup of an aliquot.

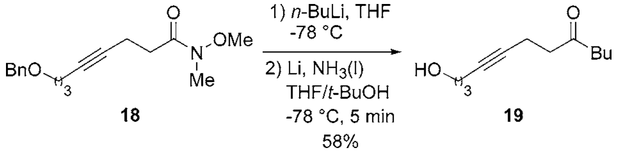
(4) (a) Shirai, F.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6461−6464. (b) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S.-I. *Tetrahedron* **1989**, *45*, 1327−1336. (c) Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Narisano, E.; Riva, R. *Tetrahedron* **1994**, *41*, 11967−11982. (d) Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, 914−918.

ing α- and β-hydroxy ketones **14** and **15** in satisfactory yields (58−59%) (Table 2, entries 2 and 3), which demonstrated that the relative position of the benzyl ether and the amide function has no bearing on the success of the alkylation/debenzylation process. In the case of compound **10** with its tertiary *O*-benzyl ether, the expected hydroxy ketone **16** was isolated in poor yield (16%), and the diol **17** was obtained in 51% yield. However, when the Birch reduction step was carried out without *t*-BuOH, the yield of **16** was raised to 92% (Table 2, entries 4 and 5).

We have also shown that *p*-methoxybenzyl and trityl ethers can be reduced using the same process. Indeed, treatment of amides **11** and **12** under the optimized conditions proceeded smoothly and provided the expected hydroxy ketones **2** and **13** in 74 and 70% yields, respectively (Table 2, entries 6 and 7).

The aforementioned nucleophilic addition/Birch reduction process is very chemoselective as alkynes are not reduced. When the acetylenic amide **18** was treated with *n*-BuLi in THF at −78 °C and the resulting tetrahedral intermediate of type **II** was added to a solution of Li, NH_3(l) in the presence of *t*-BuOH (−78 °C, 5 min), the acetylenic hydroxy ketone **19** was isolated in 58% yield (Scheme 4). Under these specific conditions, no trace of alkene was detected by GC/MS or ^{1}H NMR spectral analysis of the crude reaction mixture. By way of contrast, when the reduction step was carried out at −33 °C with extended reaction times, a partial reduction of the alkyne and an over-reduction of the ketone to the corresponding alcohol were observed.

Scheme 4. Consecutive Alkylation/Birch Reduction Process of an Acetylenic Weinreb Amide



In conclusion, we have shown that the stable tetrahedral intermediate **II** that results from the addition of an organometallic reagent to a Weinreb amide can efficiently serve as a latent carbonyl protecting group and enable a subsequent chemoselective deprotection of various protecting groups (Bn, PMB, Tr) via the Birch reduction. This general and reliable protocol provides direct access to various hydroxy ketones in good yields from Weinreb amides. Application of this methodology to the synthesis of natural products such as (+)-zoapatanol is reported in the following paper.

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Supporting Information Available: General experimental procedure and characterization data of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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