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Dialkylaluminum *N*,*O*-Dimethylhydroxylamine Complex as a Reagent to Mask Reactive Carbonyl Groups in Situ from Nucleophiles

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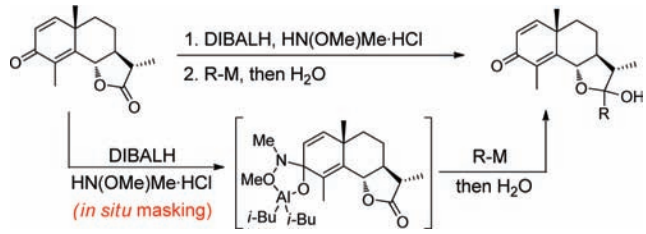
ABSTRACT



Aluminum complexes of *N*,*O*-dimethylhydroxylamine are effective reagents to mask carbonyl groups in situ from nucleophilic addition by organolithiums, Grignard reagents, and borohydrides. The utility of this process by selectively adding nucleophiles into carbonyl groups on a variety of structures as well as distinguishing between carbonyl groups on a sensitive natural product is demonstrated. ^{1}H NMR analysis supports the in situ masking of the more reactive carbonyl group.

The addition of organometallic nucleophiles to Weinreb amides is a powerful strategy for the synthesis of aldehydes or ketones.[1−3] The key tetrahedral intermediate that is formed during the process is exceptionally stable and guards the trapped carbonyl precursor from nucleophilic attack. Indeed, the masked carbonyl group can be carried through additional synthetic manipulations prior to its unveiling.[4,5] Cossy and co-workers have exploited the stability of the tetrahedral intermediate using a Birch reduction following nucleophilic addition to a Weinreb amide[4] and extended this strategy to the synthesis of zoapatanol.[5] During the course of our work to produce semisynthetic derivatives of biologically active natural products, the direct addition of a nucleophile to a less reactive carbonyl group (i.e., lactone) in the presence of a more reactive carbonyl group (i.e., ketone) was necessary. Common strategies to achieve this goal require the use of protecting groups and/or reduction/oxidation sequences. However, neither of these multistep synthetic strategies were attractive to us due to poor step economy.[6] Herein we report a general strategy to mask a reactive carbonyl group in the presence of a nucleophile using complexes of dialkylaluminum and *N*,*O*-dimethylhydroxylamine.

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(1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
(2) Recent examples in synthesis: (a) Malathong, V.; Rychnovsky, S. D. *Org. Lett.* **2009**, *11*, 4220–4223. (b) Clive, D. L. J.; Pham, M. P. *J. Org. Chem.* **2009**, *74*, 1685–1690. (c) Kokotos, C. G.; Baskakis, C.; Kokotos, G. *J. Org. Chem.* **2008**, *73*, 8623–8626. (d) Yang, S.-B.; Gan, F.-F.; Chen, G.-J.; Xu, P.-F. *Synlett* **2008**, 2532–2534. (e) Pippel, D. J.; Mapes, C. M.; Mani, N. S. *J. Org. Chem.* **2007**, *72*, 5828–5831. (f) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408–3419. (g) Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427–1429.
(3) Recent preparations of Weinreb amides: (a) Davis, F. A.; Theddu, N. *J. Org. Chem.* **2010**, *75*, 3814–3820. (b) Krishnamoorthy, R.; Lam, S. Q.; Manley, C. M.; Herr, R. J. *J. Org. Chem.* **2010**, *75*, 1251–1258. (c) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 3689–3697.
(4) Taillier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2145–2147.
(5) Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097–2108.

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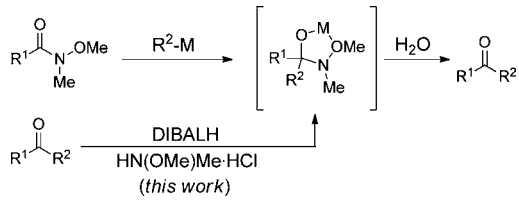
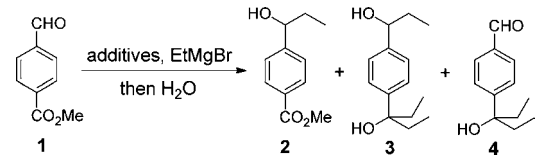
The trapping of carbonyl groups with lithium amides has been advocated by Comins,[7] but the major drawback is that lithium amides are strong bases. So deprotonation is a major side reaction, if acidic protons are present. Hoffman and co-workers have used the lithiated amide derivative of *N*,*O*-dimethylhydroxylamine to mask an aldehyde from reduction.[8] This process was successful on a single substrate but failed on more complex systems due to unavoidable deprotonation at other sites.[9] Lithium *N*,*O*-dimethylhydroxylamide was subsequently used to protect aromatic aldehydes where α-deprotonation is not an issue.[10] To our knowledge, no other general strategies to mask reactive carbonyl groups to nucleophiles as tetrahedral intermediates with *N*,*O*-dimethylhydroxylamines are known.[11] We have found that aluminum complexes of *N*,*O*-dimethylhydroxylamine are powerful and versatile reagents to mask reactive carbonyl groups in the presence of nucleophiles without the drawback of high basicity associated with lithium amides (Scheme 1).

Scheme 1. Strategies to Trap Carbonyl Groups in Situ



To determine the feasibility of this strategy, we selected methyl 4-formylbenzoate **1** as a substrate, because it has two different types of carbonyl groups (Table 1). The addition of 1 equiv of EtMgBr occurs at the aldehyde to give adduct **2**, and the addition of excess Grignard reagent consumes both carbonyl groups to provide the diol **3**. We hypothesized that using a combination of DIBALH and HN(OMe)Me•HCl, the more reactive carbonyl group would be masked in situ as an aminal and protected from the subsequent nucleophilic attack. Accordingly, upon pretreatment of **1** with a combination of DIBALH and HN(OMe)Me•HCl, the major product isolated after adding EtMgBr was the aldehyde **4** resulting from selective double addition to the less reactive carbonyl group (i.e., the ester). Further optimizations lead to the conclusion that the first equivalent of Grignard reagent removes the last proton attached to the amine (the first acidic proton of the amine hydrochloride is consumed by DIBALH) and fully stabilizes the aminal from nucleophilic addition.

Table 1. Optimization of in Situ Carbonyl Group Masking



			yield (%)[a]			
entry	additives	EtMgBr	**1**	**2**	**3**	**4**
1	none	1 equiv	10	49	0	0
2	none	6 equiv	0	0	82	0
3	DIBALH, HN(OMe)Me•HCl	5 equiv	0	0	0	47
4	DIBALH, HN(OMe)Me•HCl then *i*-PrMgCl (1 equiv)	4 equiv	0	0	0	67

[a] Isolated yields.

Thus, we turned our attention to *i*-PrMgCl as a base,[12] and this strategy not only spared an additional equivalent of nucleophile but also increased the isolated yield of **4** to 67% (entry 4).

To determine the scope of this strategy, we explored compounds **1** and **5**−**8** as substrates because each has two different types of carbonyl groups (Table 2). Indeed, using our optimized protocol to mask the more reactive carbonyl group followed by addition of an organolithium, a Grignard reagent, or borohydride as a nucleophile, selective addition to the less reactive carbonyl group was observed. Specifically, for substrate **1**, the double addition of *n*-BuLi, MeMgBr, or EtMgBr occurrs preferentially at the ester group after pretreatment with the dialkylaluminum complex. In the cases of the Grignard additions, the use of THF lead to lower yields due to unwanted carbonyl reduction; however, this competing process was eliminated using Et_2O as the primary solvent.[13] The synthetic utility of Grignard reagents continues to grow due to recent advances in the preparation of magnesium compounds.[12,14] Super hydride proved to be the optimum reagent to promote reduction of ester **1**, and the aldehyde was returned after aqueous workup. This strategy was subsequently applied to substrates **5**−**6** bearing a ketone and ester and substrates **7**−**8** with an aldehyde and ketone. Synthetically useful yields were rountinely isolated, and in each case, the more reactive carbonyl groups were unscathed. This strategy using aluminum complexes represents a significant advance because it is fully compatible with ketones and other carbonyl groups with acidic α-protons, unlike previous protocols.[8−10] Another application is the one-step preparation of 5-hydroxy-5-methylhexan-2-one (**12**)

(6) (a) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201. (b) Young, I. S.; Baran, P. S. *Nature Chem.* **2009**, *1*, 193–205.

(7) Comins, D. L. *Synlett* **1992**, 615–625.

(8) Hoffmann, R. W.; Munster, I. *Tetrahedron Lett.* **1995**, *36*, 1431–1434.

(9) Kruger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499–7504.

(10) Roschangar, F.; Brown, J. C.; Cooley, B. E.; Sharp, M. J.; Matsuoka, R. T. *Tetrahedron* **2002**, *58*, 1657–1666.

(11) Titanium tetrakis(dialkylamides) are known to protect carbonyl groups in situ. Reetz, M. T.; Wenderoth, B.; Peter, R. *J. Chem. Soc., Chem. Commun.* **1983**, *8*, 406–408.

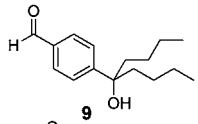
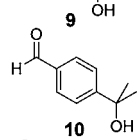
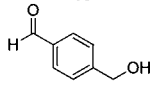
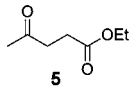
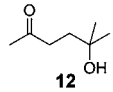
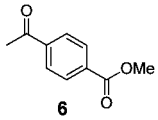
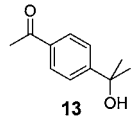
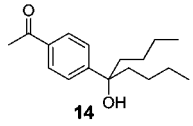
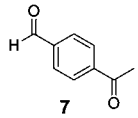
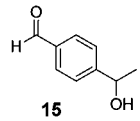
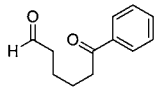
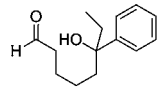
(12) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958–2961.

(13) For an example of carbonyl reduction with a Grignard reagent, see: Hoye, T. R.; Aspaas, A. W.; Eklov, B. M.; Ryba, T. D. *Org. Lett.* **2005**, *7*, 2205–2208.

(14) Fleury, L. M.; Ashfeld, B. L. *Tetrahedron Lett.* **2010**, *51*, 2427–2430.

Table 2. Selective Additions to Carbonyl Groups

substrate **1, 5–8** → (1. DIBALH, HN(OMe)Me·HCl; 2. *i*-PrMgCl, R-M, then H_2O) → product **9–16**

entry	substrate	R-M	major product	yield[a]
1	**1**	*n*-BuLi[b]	 **9**	87%
2	**1**	MeMgBr	 **10**	70%
3	**1**	$LiBEt_3H$[b]	 **11**	78%
4	 **5**	MeLi[b]	 **12**	65%
5	 **6**	MeLi[b]	 **13**	83%
6	**6**	MeMgBr[b]	**13**	76%
7	**6**	*n*-BuLi[b]	 **14**	60%
8	 **7**	MeLi	**10**	63%
9	**7**	MeMgBr	**10**	86%
10	**7**	$LiBEt_3H$	 **15**	86%
11	 **8**	EtMgBr	 **16**	68%

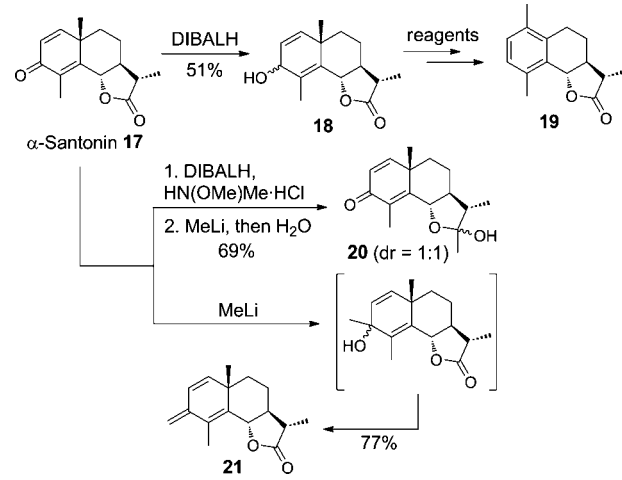
[a] Isolated yields. [b] *i*-PrMgCl was not used as a base prior to the addition of the nucleophile.

from ethyl levulinate (**5**) in 65% yield because **12** is routinely used in synthesis, but existing syntheses require multiple steps.[15] The nucleophiles MeLi, *n*-BuLi, MeMgBr, EtMgBr, and $LiBEt_3H$ readily participate in the reaction to provide a high level of preferential selectivity for the less reactive carbonyl group when added after DIBALH and HN(OMe)Me·HCl.

(15) (a) Masuno, H.; Yamamoto, K.; Wang, X.; Choi, M.; Ooizumi, H.; Shinki, T.; Yamada, S. *J. Med. Chem.* **2002**, *45*, 1825–1834. (b) Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* **1989**, *54*, 6001–6003.

To demonstrate a major application of this method, we turned our attention to natural products, as our research interests are the selective modification of these compounds for structure−activity investigations.[16] Typically, natural products have a diverse array of functional groups, and the significance of selectively modifying them has been recently demonstrated by others.[17,18] The sesquiterpene lactone, α-santonin (**17**), is a key scaffold that has been used on numerous occasions to build synthetic derivatives[16,19] and access other natural products.[20,21] The molecule has two carbonyl groups: (1) a highly reactive cyclic ketone and (2) a less reactive lactone. Our initial synthetic strategy was to protect the ketone as an ether and then modify the lactone (Scheme 2). Thus, DIBALH readily reduced the ketone to

Scheme 2. Nucleophilic Additions to α-Santonin (**17**)



the alcohol **18** without affecting the lactone.[19] Unfortunaetly, the next steps of this strategy proved to be quite difficult due to the facile carbon−oxygen bond cleavage that concomitantly promotes the formation of the aromatic compound **19** under a variety of conditions.[22] Because of the sensitive nature of α-santonin (**17**), a stepwise approach ultimately proved intractable, and we turned our attention to the in situ protection strategy. We treated **17** with DIBALH/HN(OMe)Me·HCl and MeLi, and the lactol **20** was produced in 69% yield (see Scheme 2). To contrast this result, the addition of only MeLi to **17** provided the unstable tertiary

(16) Han, C.; Barrios, F. J.; Riofski, M. V.; Colby, D. A. *J. Org. Chem.* **2009**, *74*, 7176–7179.
(17) Lewis, C. A.; Longcore, K. E.; Miller, S. J.; Wender, P. A. *J. Nat. Prod.* **2009**, *72*, 1864–1869.
(18) Erb, J.; Alden-Danforth, E.; Kopf, N.; Scerba, M. T.; Lectka, T. *J. Org. Chem.* **2010**, *75*, 969–971.
(19) Arantes, F. F. P.; Barbosa, L. C. A.; Alvarenga, E. S.; Demuner, A. J.; Bezerra, D. P.; Ferreira, J. R. O.; Costa-Lotufo, L. V.; Pessoa, C.; Moraes, M. O. *Eur. J. Med. Chem.* **2009**, *44*, 3739–3745.
(20) Zhang, W.; Luo, S.; Fiang, F.; Chen, Q.; Hu, H.; Jia, X.; Zhai, H. *J. Am. Chem. Soc.* **2005**, *127*, 18–19.
(21) Suzuki, T.; Miyashita, M. *Heterocycles* **2001**, *54*, 805–870.
(22) (a) T. Kawamata, T.; Nagashima, K.; Nakai, R.; Tsuji, T. *Synth. Commun.* **1996**, *26*, 139–148. (b) Banerjee, A. K.; Vera, W. *Synth. Commun.* **1996**, *26*, 4641–4646. (c) Huffman, J. W. *J. Org. Chem.* **1987**, *52*, 2901–2904.

alcohol which rapidly converted to the triene **21** during purification (77% yield). These data illustrate the effectiveness of the in situ trapping of a reactive carbonyl group with a dialkylaluminum complex because the carbonyl groups can be accessed selectively. This strategy not only avoids multistep protection/deprotection sequences but also is superior in the case of sensitive and complex natural products, such as **17**, where multistep sequences can not be used.

To gain further insight into the process, we treated substrate **1** with DIBALH/HN(OMe)Me•HCl in THF and acquired ^{1}H NMR data at rt (Figure 1). Because we were only interested in the protons downfield, these data were quickly gathered using the "no-D" NMR method.[23] Comparisons of the spectra of substrate **1** with treated **1** show that the proton of the aldehyde at 9.34 ppm is no longer present when the dialkylaluminum reagent is added. Also, the protons on the aromatic ring have shifted, likely due to the absence of the carbonyl group of the aldehyde after addition of the reagent.

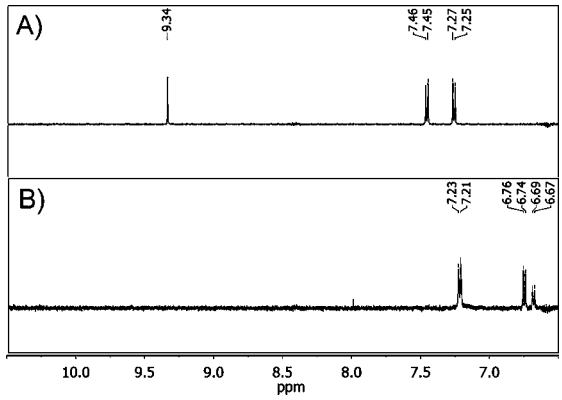


Figure 1. Comparison of ^{1}H NMR data of compound **1** at 500 MHz. (A) Compound **1** in THF. (B) Compound **1** in THF after treatment with DIBALH/HN(OMe)Me•HCl.

In conclusion, we have demonstrated a general strategy to trap reactive carbonyl groups with aluminum complexes of *N*,*O*-dimethylhydroxylamine. This protocol is a significant advancement over previously described lithium amides because competing deprotonation with the strongly basic lithium amides is limited. We have demonstrated the scope of this process by selectively adding nucleophiles into carbonyl groups on a variety of structures. We have applied our strategy to distinguish selectively between carbonyl groups on a sensitive natural product in which multistep strategies fail. Additionally, we have provided key NMR data to support the in situ masking of the more reactive carbonyl group. Overall, this process is a powerful alternative to traditional multistep reduction/oxidation processes and protection/deprotection strategies to distinguish between reactive carbonyl groups on natural products and other complex molecules.

Acknowledgment. We are grateful to Purdue University for funding. X.Z. is the recipient of a Dean's Summer Fellowship.

Supporting Information Available: Full experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For a leading reference, see Hoye, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567–2570.