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Synthesis of Ketones and Aldehydes *via* Reactions of Weinreb-Type Amides on Solid Support[1]

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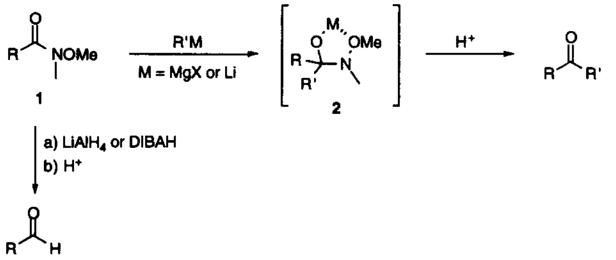
Abstract: Ketones and aldehydes were formed in low to good yields in reactions of Weinreb-type amides on solid support and no overaddition occurred.

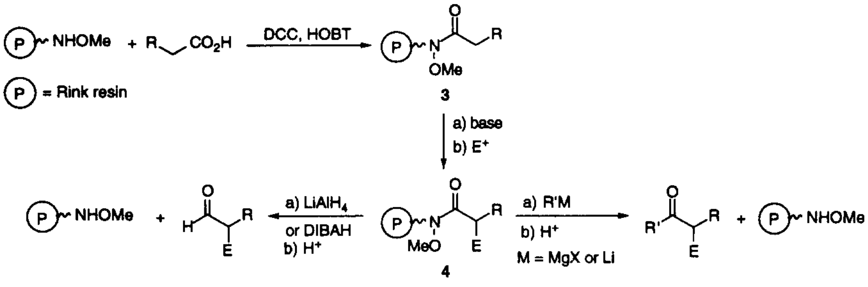
The rapid synthesis of a wide variety of compounds greatly facilitates the discovery of biologically active agents.[2] The ability to generate libraries of commercially unavailable ketones and aldehydes is a valuable tool in this process. Moreover, these customized libraries may be used as inputs in other libraries (e.g., those of Ugi four-component condensations[3]). This research focuses on the creation of aldehyde and ketone diversity by performing reactions with Weinreb-type amides on solid support.

Weinreb amides (1) display remarkable selectivity in their reactions with simple organometallic reagents (Eq. 1).[4] These *N*-methoxy-*N*-methylamides react with Grignard species, organolithium species, $LiAlH_4$, or DIBAH to afford ketones or aldehydes in high yields. Little or no overaddition occurs presumably due to chelation of the Lewis acid with the erstwhile carbonyl oxygen and the *N*-methoxy oxygen (2), the stable intermediate decomposing to the ketone or aldehyde upon treatment with acid.



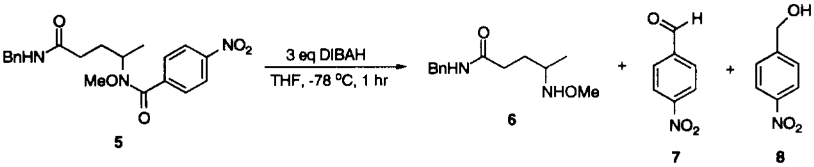
(1)

Ketones and aldehydes are envisioned to be generated from reactions of Weinreb-type amides on solid support (Scheme 1). The *N*-Me group in Weinreb amides is replaced by a linker that attaches the methoxyamine to a polymer (Rink[5] in this case). One source of diversity is the different carboxylic acids which can be coupled to the polymer-bound methoxyamine. A second source of diversity is enolate alkylation of Weinreb-type amide **3** with different electrophiles. A third source of diversity is reacting Weinreb-type amide **4** with different simple organometallic reagents to produce ketones or aldehydes. Another noteworthy feature of this chemistry is that it potentially regenerates the polymer-bound methoxyamine.



Scheme 1

The chemistry of Weinreb-type amides with a 2° *N*-alkyl group was tested in solution. DIBAH reduction of amide **5**[6,7] cleanly provided methoxyamine **6**, aldehyde **7**, and alcohol **8** in a 2.3:1:1.3 ratio (Eq. 2). MeMgCl cleanly converted amide **9** to amine **6** and ketone **10** with no overaddition (Eq. 3). However, in most



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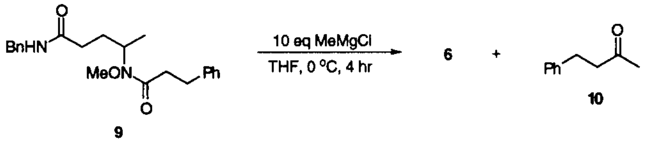
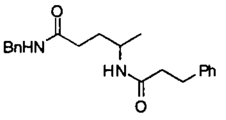


(3)

reactions of amide **9** with EtMgBr, ⁿBuLi, PhMgCl, and PhLi at various temperatures, the major product was non-*N*-methoxy amide **11**!



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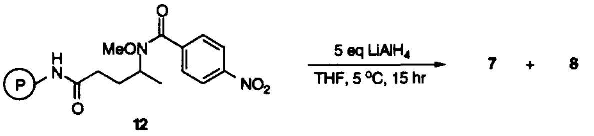
Reactions of polymer-bound Weinreb-type amides with a 2° *N*-alkyl group were conducted concurrently. $LiAlH_4$ cleanly reduced amide **12** to aldehyde **7** and alcohol **8** in a 1:1.4 ratio (Eq. 4). However, the major reaction in the treatment of amide **13** with MeMgCl was N-O bond cleavage (Eq. 5). It was conjectured that *N*-O bond cleavage by Grignard and organolithium reagents in solution and solid phases might have been caused by the α–Me branch in the 2° *N*-alkyl group interfering with carbonyl addition.

Synthesis of a Weinreb-type amide with a 1° *N*-alkyl linker to the Rink resin is exemplified in Scheme 2. Hydrocinnamic acid was transformed to its *N*-methoxyamide (**14**),[8] which underwent Michael addition to methyl acrylate in the presence of catalytic ᵗBuOK.[9] Hydrolysis of amideester **15** furnished the acid which was then coupled to the Rink resin. A general polymer-bound methoxyamine linker (see Scheme 1) may be



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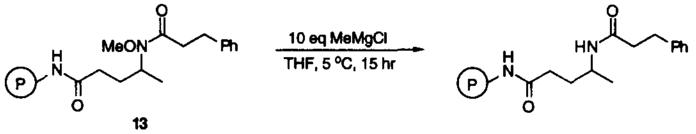
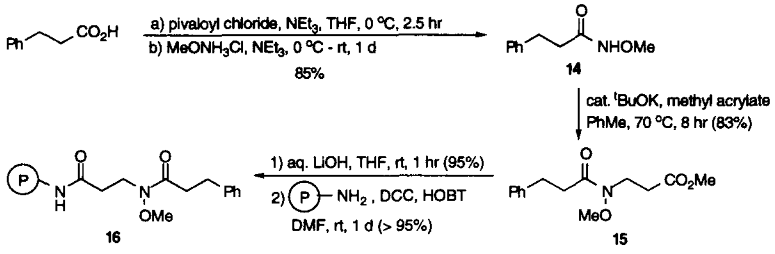


(5)

synthesized by replacing hydrocinnamic acid with a nitrogen protecting group in Scheme 2. After the *N*-protected 3-(*N*-methoxyamino)propanoic acid is coupled to the resin, removal of the protecting group affords the methoxyamine linker.



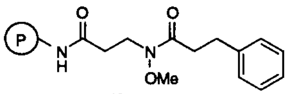
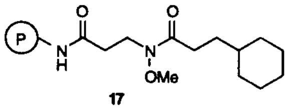
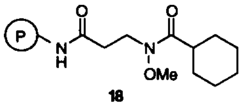
Scheme 2

Results of reactions of polymer-bound Weinreb-type amides with a 1° *N*-alkyl linker are presented in Table 1. MeMgCl reactions with amides **16** and **17** furnished clean crude products of the methyl ketones in good yields. The product yields of the other Grignard reactions[10] ranged from low to relatively good and those of the three $LiAlH_4$ reactions[11] were low. In all reactions, no overaddition and no N-O bond cleavage were observed. Furthermore, β-elimination producing *N*-methoxyamides did not transpire. The product yields might have been adversely affected by side reactions involving the classical amide bond. This problem can be obviated by substituting an ether bond for the classical amide bond.

The procedure for the MeMgCl reaction of Weinreb-type amide **17** is representative. To a suspension of amide **17** (0.015 mmol) in THF (0.6 mL) was added MeMgCl (70 μL in THF, 0.22 mmol). The flask was glass-stoppered and parafilmed and the mixture was stirred for 13 hr at rt. The mixture was then quenched with 5% HCl/EtOH (0.5 mL) and stirred for 30 min at rt. The resin was filtered and washed alternately with 3 X 0.5 mL EtOH and 3 X 1 mL CH_2Cl_2. After the filtrate was extracted with CH_2Cl_2 and H_2O, the crude product was clean for 4-cyclohexyl-2-butanone (1.8 mg, 78% yield).[12]

Reactions of Weinreb-type amides on solid support potentially permit the synthesis of libraries of aldehydes and ketones. Nearly all the ketones in Table 1 are not commercially available and the crude ketone products are of sufficient purity to be used in subsequent reactions. For instance, synthesis of focused Ugi-derived libraries utilizing non-commercial ketone inputs is currently underway.

Table 1. Reactions of Weinreb-Type Amides on Solid Support[a]

	MeMgCl[b]	homoallylMgBr[b]	BnMgCl[b]	PhMgCl[c]	$LiAlH_4$[d]
 **16**	77%	46%	23%	33%	10%
 **17**	78%	62%	23%	59%	11%
 **18**	16%	28%	27%	—	15%

[a] The percent numbers shown are the yields of ketone or aldehyde products. No alcohol was detected in any reaction. The yields are based on the ^{1}HMR integration of the products relative to that of TMS of known concentration.

[b] 1) 15 eq Grignard reagent, THF, rt, 15 hr, 2) 5% HCl/EtOH, rt, 30 min.

[c] 1) 15 eq PhMgCl, THF, 60 °C, 15 hr, 2) same workup.

[d] 1) 5 eq $LiAlH_4$, THF, 5 °C, 15 hr, 2) same workup.

Acknowledgement

Financial support from NIH Grant GM51095 is greatly appreciated.

References and Notes

1. 209th ACS National Meeting in Anaheim, CA on April 3, 1995: Abstracts of Papers, Part 2, Organic Division, 145. Synthesis of C-terminal peptide aldehydes by reactions of $LiAlH_4$ with Weinreb-type amides on solid support was recently published: Fehrentz, J.-A.; Paris, M.; Heitz, A.; Velek, J.; Liu, C.-F.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1995**, *36*, 7871-7874.
2. For recent reviews, see: a) Felder, E. D. *Chimia* **1994**, *48*, 531-541. b) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251 and 1385-1401.
3. For a review, see: Gokel, G.; Ludke, G.; Ugi, I. Four-Component Condensations and Related Reactions. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; pp. 145-199.
4. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
5. Rink (from Advanced ChemTech) was employed because the conditions for cleavage of material off the resin are relatively mild: 15% TFA/CH_2Cl_2, rt, 10 min.
6. Weinreb-type amide **5** was synthesized from levulinic acid in four steps in good overall yield: 1) $BnNH_2$, DCC, HOBT, CH_2Cl_2, rt, 1d; 2) $MeONH_3Cl$, NaOAc, MeOH, 65 °C, 15 hr; 3) BH_3·pyr, EtOH, 10% aq. HCl, - 5 °C - rt, 30 min; 4) paranitrobenzoyl chloride, NEt_3, CH_2Cl_2, rt, 1 hr.
7. All compounds in this paper had satisfactory ^{1}HMR data.
8. Miknis, G. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 536-547.
9. Darwish, I. S.; Patel, C.; Miller, M. J. *J. Org. Chem.* **1993**, *58*, 6072-6075.
10. In the crude products of some reactions, impurities arising from the Grignard reagents' reaction with the THF solvent were observed.
11. $LiAlH_4$ was used because it gave better results than DIBAH.
12. In the $LiAlH_4$ reactions in Table 1, filtering and washing the unquenched resin with dry THF resulted in no aldehyde product in the filtrate. By contrast, in the PhMgCl reaction of Weinreb-type amide **16**, most of the ketone product was found in the supernatant of the reaction mixture, a smaller amount of the ketone was obtained after the resin was rinsed with dry THF in the reaction flask, and no ketone was detected after the resin was quenched with acid! This peculiar behavior will be explored further.

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