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Improved syntheses of α-BOC-aminoketones from α-BOC-amino-Weinreb amides using a pre-deprotonation protocol

Jinchu Liu,* Norihiro Ikemoto,* Daniel Petrillo and Joseph D. Armstrong, III

Process Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

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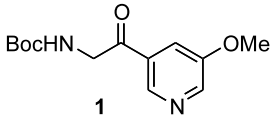
Abstract—A general procedure was developed to prepare α-BOC-aminoketones in good yields from α-BOC-amino Weinreb amides containing an exchangeable amino proton. By first deprotonating this amino group using 1 equiv. of a simple alkyl Grignard base, only a stoichiometric amount, rather than a large excess, of the nucleophile was needed to prepare the ketone. This procedure is therefore more economical to run and the purification is easier.

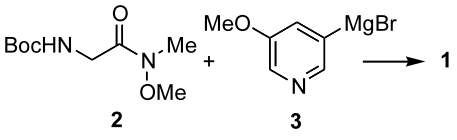
Weinreb amides (*N*-methoxy-*N*-methylamides) are useful precursors to ketones. When they are allowed to react with Grignard or organolithium reagents, stable, metal-chelated tetrahedral intermediates are formed, which resist further nucleophilic attack. Formation of alcohol side products is therefore minimized.[1] Weinreb amides that contain an α-BOC-amino group have been used to access α-BOC-aminoketones, which are intermediates in the syntheses of many drugs and biologically active compounds.[2]

We recently required multi-kg quantities of the α-BOC-aminoketone **1** (Fig. 1), an intermediate to an HIV protease drug candidate. This intermediate was prepared initially by reacting the Weinreb amide **2** with >2 equiv. of Grignard reagent **3** (Scheme 1). Excess reagent was required because the deprotonation of the exchangeable amino proton of **2** was faster than the nucleophilic attack at the Weinreb amide functional group. Thus, when only 1.2 equiv. of reagent **3** was used, only a trace amount of **1** was isolated, along with recovered **2** and 3-methoxypyridine by-product.



1

Figure 1.



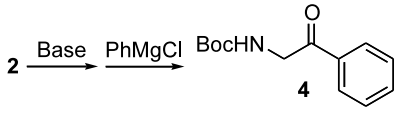
2 **3**

Scheme 1.

For scale-up work, the use of excess Grignard reagent **3** was impractical. First, this reagent was not commercially available and had to be prepared from expensive 3,5-dibromopyridine in two steps. Second, this made purification of **1** difficult due to the formation of large amounts of 3-methoxypyridine by-product.

It was reasoned that pre-deprotonation of the amino group using an inexpensive base whose by-product is easily removed, followed by the addition of a stoichiometric amount of nucleophile **3**, should avoid these problems. Thus, by first adding a little less than 1

Table 1. Comparison of bases



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Entry	Base	Yield (%)
1	*i*-PrMgCl	96
2	MeMgCl	99
3	*n*-BuLi	32
4	*s*-BuLi	44

* Corresponding authors.

0040-4039/02/$ - see front matter
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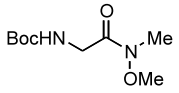
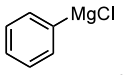
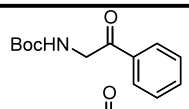
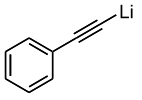
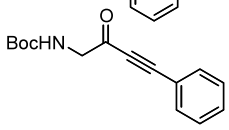
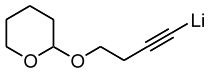
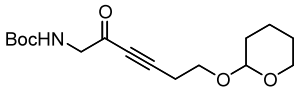
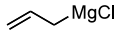
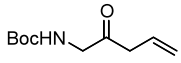
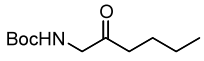
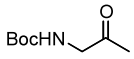
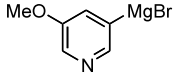
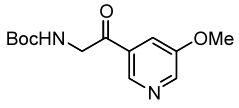
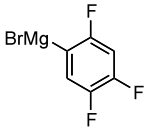
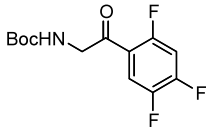
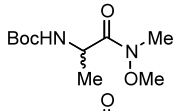
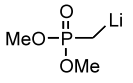
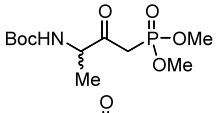
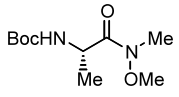
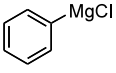
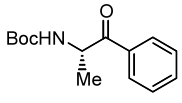
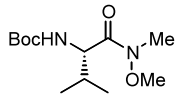
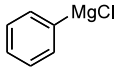
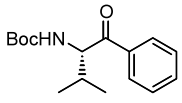
equiv. of *i*-PrMgCl/THF, followed by 1.0 to 1.25 equiv. of Grignard reagent **3**, a good yield of BOC-aminoketone **1** was obtained with much less of 3-methoxypyridine by-product. After work-up, the α-BOC-aminoketone **1** was crystallized out of the organic solution with good purity, thus eliminating the chromatographic purification. Multi-kg quantities of **1** were prepared successfully using this procedure.

A literature search revealed that aminoketones are prepared typically using excess amounts of nucleophiles when an exchangeable amino proton is present in their BOC- or CBZ-protected amino-Weinreb amide precursors.[2–5] Some of these Grignard or organolithium reagents are neither commercially available nor trivial to prepare.[3a,c,d,5,6] Furthermore, the purification was difficult in many cases, especially when the desired

Table 2. Preparation of α-Boc-aminoketones[a]

Entry	Substrate	Base	Nucleophile	BOC-Aminoketone	Yield[b]
1		i-PrMgCl			96%
2	"	i-PrMgCl			84%
3	"	MeMgCl			73%
4	"	MeMgCl			98%
5	"	$Me(CH_2)_3MgCl$	$Me(CH_2)_3MgCl$		80%
6	"	MeMgCl	MeMgCl		92%
7	"	i-PrMgCl			87%
8	"	i-PrMgCl			73%
9		MeMgCl			83%
10		i-PrMgCl			97%
11		MeMgCl			99%

a) The BOC-aminoketone examples in this table are previously reported compounds except for entries 2, 7 and 8, which are characterized as follows. **Entry 2**: M.p. 53 °C. ^{1}H-NMR (400 MHz, CDCl3): δ 1.47 (s, 9H), 4.25 (d, J = 5.0 Hz, 2H), 5.24 (s, broad, 1H), 7.38~7.47 (m, 2H), 7.48~7.51 (m, 1H), 7.58~7.60 (m, 2H). ^{13}C-NMR (100 MHz, CDCl3): δ 28.3, 52.2, 80.1, 85.8, 93.9, 119.4, 128.7, 131.1, 133.2, 155.5, 183.2. **Entry 7**: M.p. 112 °C. ^{1}H-NMR (400 MHz, CDCl3): δ 1.46 (s, 9H), 3.90 (s, 3H), 4.65 (d, J = 4.6 Hz), 5.50 (s, broad, 1H), 7.68 (dd, J = 2.9, 1.7 Hz, 1H), 8.50 (d, J = 2.9 Hz, 1H), 8.75 (d, J = 1.0 Hz, 1H). ^{13}C-NMR (100 MHz, CDCl3): δ 28.2, 47.8, 55.7, 80.0, 117.5, 130.5, 141.2, 143.5, 155.6, 155.9, 193.7. **Entry 8**: M.p. 91 °C. ^{1}H-NMR (400 MHz, CDCl3): δ 1.47 (s, 9H), 4.56 (s, 2H), 5.42 (s, 1H), 7.02~7.09 (m, 1H), 7.81~7.88 (m, 1H). ^{13}C-NMR (100 MHz, CDCl3): δ 28.0, 51.2 (d, J = 13.3 Hz), 79.7, 106.6 (dd, J = 30.0, 21.2 Hz), 118.2 (ddd, J = 20.3, 4.6, 2.1 Hz), 119.4 (dt, J = 16.6, 3.8 Hz), 147.1 (ddd, J = 248.3, 12.8, 3.1 Hz), 153.8 (ddd, 261.2, 15.2, 12.8 Hz), 155.6, 157.9 (dd, J = 254.9, 9.5 Hz), 190.8 (d, J = 5.7 Hz).

b) Isolated yields after purification via crystallization or flash chromatography.

product is unstable to chromatography.[5b,7] Thus, further study and development of our pre-deprotonation protocol appeared warranted.

The choice of base was studied first, using the conversion of **2** to the phenylketone **4** as a test reaction (Table 1). The four bases shown were chosen because they are readily available and have by-products that are volatile and easily removed. The Grignard reagents, MeMgCl/THF and *i*-PrMgCl/THF, gave high yields of **4** when 0.98 equiv. were added first to the Weinreb amide **2** at <−5°C, followed by 1.2 equiv. of phenyl Grignard. The lithium bases, *n*-BuLi/hexane and *s*-BuLi/hexane, on the other hand, gave poor yields and more unidentified impurities under the same reaction conditions. Adding 1 equiv. of $MgBr_2$–Et_2O to the reaction mixture between the *s*-BuLi and the phenyl Grignard charges did not improve the yield. It was subsequently found that the Weinreb amide **2** is unstable to the lithium bases even at −15 to −10°C, while it is completely stable in the presence of Grignard bases. Thus, after base addition followed by work-up, the Weinreb amide **2** was recovered in 99% yield using *i*-PrMgCl/THF but only in 54% yield with *n*-BuLi/hexane.

Using either MeMgCl/THF or *i*-PrMgCl/THF as the base, we then studied the reactivities of several lithium and magnesium nucleophiles with BOC-glycine Weinreb amide **2**, as well as its α-methyl and isopropyl derivatives (Table 2). Slightly less than 1 equiv. of base was added to the Weinreb amide, followed by 1.1 to 1.26 equiv. of nucleophile. The reaction was followed by HPLC or TLC, and when most of the Weinreb amide had been converted, the reaction was worked up and the desired ketone was purified.[8] Some organolithium reagents that are unstable (entries 3 and 9) were generated at low temperature following published procedures.[6a,9] For these examples, a pre-cooled solution of the deprotonated Weinreb amide was added to a solution of these reagents (−60°C), and the resulting mixture was allowed to warm slowly to room temperature over several hours.

With these procedures, a variety of ketones were prepared readily in good to excellent yields using aryl, alkynyl and primary alkyl nucleophiles. These yields are as good as those reported for the corresponding reactions using excess nucleophilic reagents.[2g,6] Purification was comparatively easier, because less by-products were produced. With our pre-deprotonation protocol, ketone intermediates were prepared containing functional groups that can be elaborated to more complex target structures (entries 2, 3, 4, and 9). Furthermore, the method can be applied to chiral Weinreb amides (entries 10 and 11) to provide optically pure ketones (>99% ee) without racemization.[10]

Primary alkyl Grignard reagents reacted readily with the Weinreb amide **2** (Table 2), while secondary alkyl nucleophiles did not. After treating **2** with 2.3 equiv. of *i*-PrMgCl/THF at room temperature for three days, the Weinreb amide **2** was recovered in 48% yield with no desired isopropylketone. After pre-deprotonation of **2** with *i*-PrMgCl followed by addition of *s*-BuLi/hexane as the nucleophile, a poor yield (20%) of the corresponding ketone was isolated after 1 day at room temperature. Therefore, the reactivity of Weinreb amides appears to be restricted to primary alkyl reagents. In fact, our survey of the literature did not uncover any examples in which a Weinreb amide was reacted successfully with a secondary alkyl nucleophile.

In summary, a pre-deprotonation strategy was applied to Weinreb amides containing an exchangeable amino group. It was demonstrated that primary alkyl, aryl and alkynyl nucleophiles could be added to afford the corresponding ketones in high yields. There was very little waste since only a small excess of these nucleophiles was used. By minimizing the formation of their by-products, purification of the desired ketones was made easier. This simple procedure is an improvement over the procedures that are typically reported in the literature that employ a large excess of nucleophiles and should see general utility in cases when exchangeable protons are present in the molecules.

Acknowledgements

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8. **Typical procedure for preparation of BOC-α-aminoketone**: BOC-glycine Weinreb amide **2** (2.18 g, 10.0 mmol) was dissolved in 20 mL of dry THF, degassed and inerted under N_2. The solution was cooled to −15 to −10°C and to the resulting slurry was charged 4.9 mL of 2.0 M *i*-PrMgCl/THF (9.8 mmol) dropwise at −15 to −5°C to afford a clear solution. After cooling to <−10°C, 6.3 mL of 2.0 M PhMgCl/THF (12.6 mmol) was added at <−5°C. The cooling bath was removed, and the mixture was allowed to warm to rt over 30 min. After a 4 h age at rt, the reaction was complete. The mixture was cooled over an ice bath and 23 mL of 1.0N HCl was added slowly at <20°C, followed by 25 mL of EtOAc. The aqueous layer was cut, and the organic layer was washed with 25 mL of water and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 2.70 g oil, which solidified on standing. After flash chromatography (silica gel, 3:1 hexane/EtOAc), 2.25 g of BOC-aminoacetophenone was obtained as a white crystalline solid in 96% yield.
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10. The optical purity was determined by chiral HPLC: Chiralcel OJ (25 cm×4.6 mm), 1% EtOH/heptane, 1.5 mL/min, 20°C, 254 nm.