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Synthesis of modified Weinreb amides: *N-tert*-butoxy-*N*-methylamides as effective acylating agents

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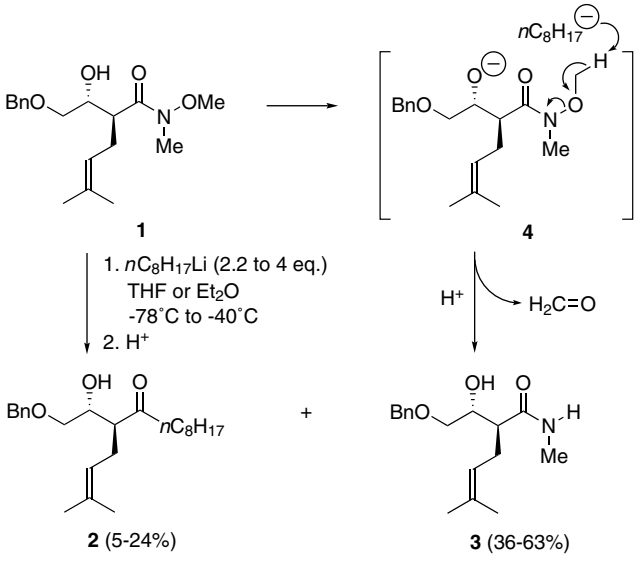
Abstract—An efficient preparation of *N*-methyl-*O-tert*-butylhydroxylamine hydrochloride has been settled, which allowed the synthesis of modified Weinreb amides. Nucleophilic addition of organolithium and Grignard reagents on these *N-tert*-butoxy-*N*-methylamides afforded efficiently the corresponding ketones and reduction with DIBAL furnished the corresponding aldehydes in good yields up to 97%.

N-Methoxy-*N*-methylamides[1] (commonly named Weinreb amides) are important carbonyl equivalents, which have been extensively used for the preparation of ketones and their synthetic utility has been widely demonstrated.[2–4] In the course of our studies on the synthesis of (−)-isoavenaciolide,[5] a naturally occurring secondary metabolite exhibiting antifungal activity,[6] we needed β-hydroxy ketone **2**, which could result from nucleophilic addition of *n*-octyllithium on Weinreb amide **1** (Scheme 1).

However, whatever the conditions (various solvents, temperatures or number of equivalents of *n*-octyllithium), the desired ketone **2** was obtained in only 5–24% yield. The main product of the reaction was *N*-methylamide **3** (36–63% yield). Formation of **3** results from decomposition of intermediate **4** via an E_2 elimination reaction, which generates formaldehyde as demonstrated earlier by Graham and Scholz[7] when treating (*N*-methyl-*N*-methoxy)methoxyacetamide with lithium diisopropylamide. Similar observations have also been reported in the literature.[8]



Scheme 1.

We were thus interested in designing a modified Weinreb amide whose structure would avoid this competitive decomposition reaction, which may be a major drawback when working on elaborated compounds. For that purpose, we chose to replace the *N*-methoxy group with a *N-tert*-butoxy group as in amides **5** (Scheme 2).

To examine the usefulness of these new Weinreb amides, we had first to set up a convenient route to *N*-methyl-*O-tert*-butylhydroxylamine hydrochloride **6**, whose reaction with acid chlorides, esters or carboxylic acids **7**

Keywords: *N*-Methyl-*O-tert*-butylhydroxylamide; Acylation; Aldehydes; Ketones; Weinreb amides.
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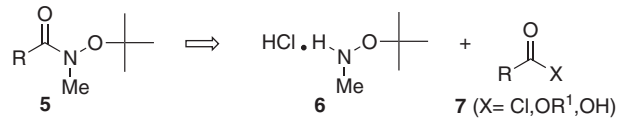
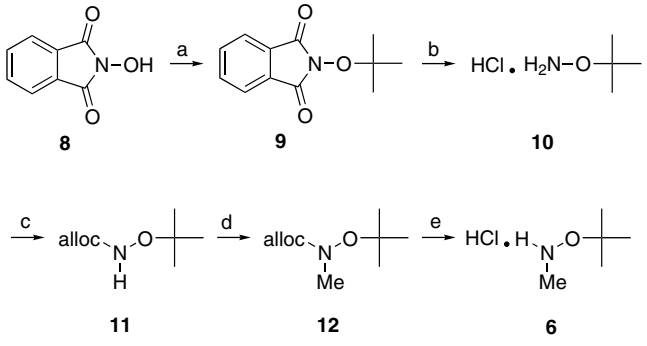


Scheme 2.

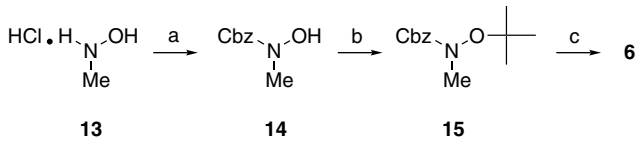


Scheme 3. Reagents and conditions: (a) AcO*t*-Bu, $HClO_4$, dioxane, rt, 40 h, 99%; (b) $H_2N–NH_2{\cdot}H_2O$, EtOH, △, 45 min then HCl, 82%; (c) allylchloroformate, pyridine, CH_2Cl_2, rt, 1 h; (d) NaH, MeI, DMF, rt, 15 h, 78% (two steps); (e) $Pd(OAc)_2$ (2.5 mol%), TPPTS (12.5 mol%), $NaBH_4$, H_2O/MeOH, rt, 1 h, then HCl, 60–70%.

would easily afford the desired amides **5**. Our initial synthesis of **6** started with *N*-hydroxyphthalimide **8**, which was treated with *tert*-butyl acetate and perchloric acid in dioxane[9] to afford *tert*-butoxyphthalimide **9** in 99% yield (Scheme 3). Deprotection of the amine using hydrazine in EtOH and acidification with HCl then furnished *O*-*tert*-butylhydroxylamine hydrochloride **10** in 82% yield. Subsequent protection of the amine using allylchloroformate, followed by *N*-methylation readily afforded compound **12** in 78% overall yield. Finally, *N*-methyl-*O*-*tert*-butylhydroxylamine hydrochloride **6** was obtained after alloc deprotection in the presence of $Pd(OAc)_2$, TPPTS and sodium borohydride[10,11] and subsequent treatment with HCl.

As this first route to *N*-methyl-*O*-*tert*-butylhydroxylamine hydrochloride **6** was a little lengthy, we devised a more straightforward synthesis starting from commercially available *N*-methylhydroxylamine hydrochloride **13** (Scheme 4).

Protection of **13** using benzylchloroformate afforded the corresponding carbamate **14**[12] in 93% yield and



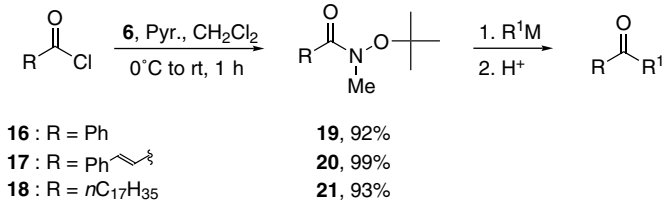
Scheme 4. Reagents and conditions: (a) benzylchloroformate, $NaHCO_3$, CH_2Cl_2, 0 °C, 0.5 h, then rt, 15 h, 93%; (b) AcO*t*-Bu, $HClO_4$, dioxane, rt, 19 h, 97%; (c) H_2, Pd/C, MeOH, HCl (MeOH), rt, 24 h, 95%.

subsequent treatment with *tert*-butyl acetate and perchloric acid led quantitatively to *N*-*O*-*tert*-butylcarbamate **15**.[13] Finally, hydrogenolysis of the carbamate moiety using Pd/C in HCl/MeOH furnished **6**[14] in quantitative yield. Thus, *N*-methyl-*O*-*tert*-butylhydroxylamine hydrochloride **6** was readily prepared in three steps and 86% overall yield from *N*-methylhydroxylamine hydrochloride **13**.

Having to hand an efficient and large-scale synthesis of **6**, we were able to examine the utility of this new amine. Thus, treatment of commercially available acid chlorides **16**–**18** with **6** in the presence of pyridine afforded amides **19**–**21** in good yields (Scheme 5). We then studied the nucleophilic addition of organolithium and Grignard reagents on these new Weinreb amides as well as reduction reactions with diisobutylaluminium hydride (Table 1).

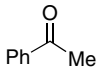
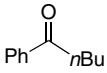
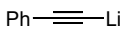
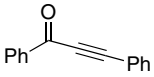
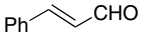
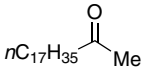
Thus, addition of methylmagnesium bromide on amide **19** afforded acetophenone in 92% yield, comparable to the yield observed with the corresponding *N*-methoxy-*N*-methylamide[1] (entry 1). Reaction of **19** with either *n*-butyllithium or lithium phenylacetylide proceeded likewise with good yields (entries 2 and 3). Reduction of amides **19**–**21** with DIBAL cleanly afforded the corresponding aldehydes in 70–83% yield (entries 4–6). Finally, addition of methylmagnesium bromide on amide **21** led to the corresponding ketone in 97% yield (entry 7). The above results illustrate the usefulness of these new Weinreb amides since all reactions proceeded in good yields, comparable to those obtained with the corresponding *N*-methoxy-*N*-methylamides (entries 1, 3, 4, and 7), and slightly higher in some cases (entries 2 ,5, and 6).

We next studied the nucleophilic addition of *n*-octyllithium on *N*-*tert*-butoxy-*N*-methyl amide **22**, an intermediate in our synthesis of (−)-isoavenaciolide (Scheme 6). The reaction afforded the expected ketone **2** with a

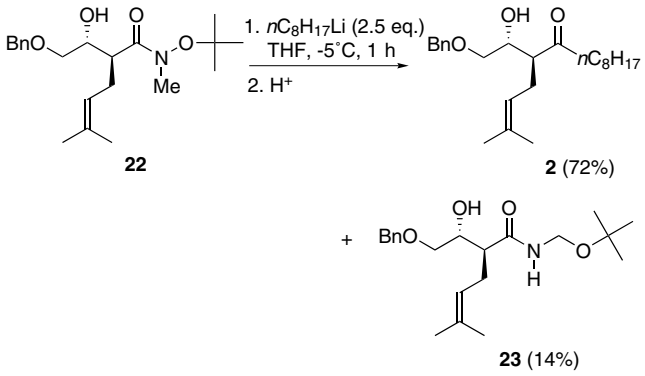


Scheme 5.

Table 1. Addition of R^1M to amides **19–21**

Entry	Amide	R^1M[a]	Equiv	T (°C)	t (h)	Product	Yield (%)
1	**19**	MeMgBr	1.1	0	1		92 (93)[b]
2	**19**	*n*-BuLi	2	0	1		91 (84)
3	**19**		1.5	rt	1		91 (90)
4	**19**	DIBAL[c]	1.5	−78	1.5	PhCHO	70 (71)
5	**20**	DIBAL[c]	1.1	−78	1.5		80 (76)
6	**21**	DIBAL[c]	1.5	−50 to −30	2	n-$C_{17}H_{35}CHO$	83 (71)
7	**21**	MeMgBr	2	0	1		97 (94)

[a] All reactions were carried out in THF on a 1 mmol scale.
[b] Yields in brackets are those reported in the literature[1] for the corresponding *N*-methoxy-*N*-methylamides.
[c] Reduction of amides **19–21** with DIBAL were carried out at low temperature to prevent the formation of the corresponding amines.



Scheme 6.

significantly improved 72% yield compared to the results obtained with *N*-methoxy-*N*-methyl amide **1** (5–24%, see Scheme 1), although a rearrangement product **23**, easily separable by flash chromatography, was also formed in this reaction (14% yield).[15]

In summary, an efficient route to *N*-methyl-*O*-*tert*-butylhydroxylamine hydrochloride **6** was devised, which allowed the preparation of the corresponding modified Weinreb amides. Nucleophilic addition of organolithium and Grignard reagents on these new *N*-*tert*-butoxy-*N*-methylamides readily afforded the corresponding ketones and hydride reduction with DIBAL delivered the corresponding aldehydes in good yields up to 97%. As demonstrated in the case of our synthesis of (−)-isoavenaciolide, the replacement of the *N*-methoxy group by a *N*-*tert*-butoxy group in Weinreb amides could be of synthetic value in organic synthesis.

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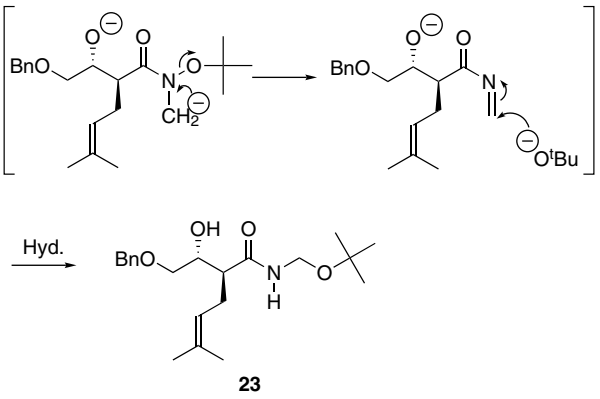
12. Characteristic data for compound **14**: R_f 0.25 (cyclohexane/AcOEt: 7:3). IR (film): 3293 (broad), 3068, 3042, 2935, 1701 (broad) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.21 (s, 3H), 5.15 (s, 2H), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 38.1, 68.1, 128.1, 128.4, 128.6, 158.1. MS (DCI/NH_3): m/z = 181 $[M + H]^+$, 199 $[M + NH_4]^+$. Anal. Calcd for $C_9H_{11}NO_3$: C 59.66, H 6.12, N 7.73, found C 59.49, H 6.15, N 7.71.
13. Characteristic data for compound **15**: R_f 0.66 (cyclohexane/AcOEt: 7:3). IR (film): 3032, 2971, 2930, 1742, 1706 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.24 (s, 9H), 3.19 (s, 3H), 5.16 (s, 2H), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.2, 41.2, 67.9, 82.0, 128.2,128.5, 136.2, 160.1. MS (DCI/NH_3): m/z = 238 $[M + H]^+$, 255 $[M + NH_4]^+$. Anal. Calcd for $C_{13}H_{19}NO_3$: C 65.80, H 8.07, N 5.90, found C 65.76, H 8.07, N 5.97.
14. Characteristic data for compound **6**: IR (KBr): 2981, 2884, 2684, 2489 cm^{-1}. ^1H NMR (CD_3OD, 200 MHz): δ 1.44 (s, 9H), 2.98 (s, 3H). ^{13}C NMR (CD_3OD, 50 MHz): δ 26.7, 37.4, 85.1. MS (DCI/NH_3): m/z = 104 $[M + H]^+$, 121 $[M + NH_4]^+$.
15. (a) For the formation of compound **23**, the following mechanism can be postulated:



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