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Reactions of Weinreb amides: formation of aldehydes by Wittig reactions

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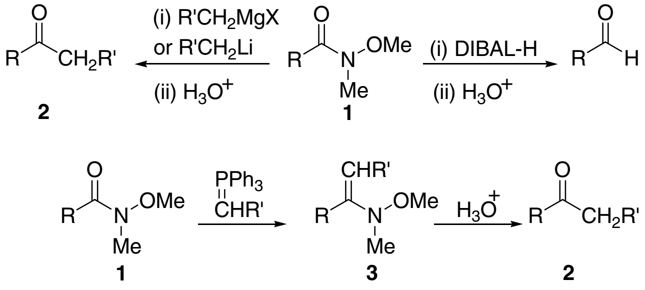
Abstract—Aldehydes are prepared in excellent yield by Wittig reactions of phosphoranes on the Weinreb amide of formic acid followed by in situ hydrolysis.

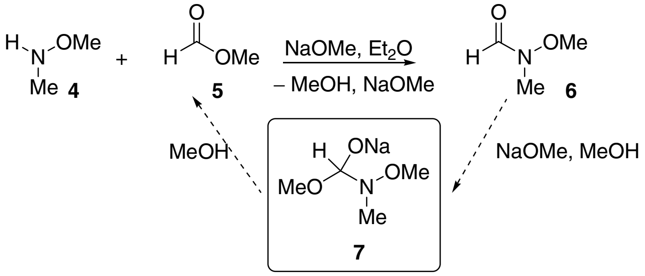
Weinreb amides (*N*-methoxy-*N*-methylamides) are very useful intermediates in synthetic organic chemistry[1] allowing the direct preparation of highly functionalised aldehydes and ketones upon reaction with appropriate nucleophiles[2] (see Scheme 1). The efficiency of this process is attributed to the intermediacy of an exceptionally stable tetrahedral intermediate,[2] which does not break down to the desired carbonyl product until work-up. Accordingly, no secondary addition of the nucleophile to this carbonyl product is seen. The stability of the intermediate has itself found elegant application,[3] providing aldehydes and ketones in masked form, allowing a second transformation to be performed chemoselectively in its presence. [Weinreb amides have also found use in chemoselective preparation of β-ketoesters[4,5] (or β-keto-Weinreb amides[5]) where ester enolates act as nucleophiles.]

Although the transformation is extremely useful, the reactivity of the organometallic reagents that react with Weinreb amides **1** must be taken into account when planning synthetic transformations. Reagents such as DIBAL-H, $LiAlH_4$, Grignard and organolithium reagents are incompatible with a number of functional groups. Hence we have sought less aggressive conditions for effecting the same transformations.

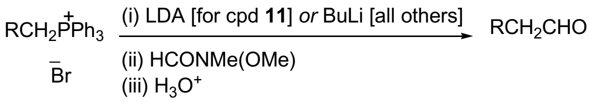
Thus, we recently reported a highly efficient alternative conversion of *N*-methoxy-*N*-methylamides **1** to related



Scheme 1.



Scheme 2.



Scheme 3.

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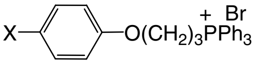
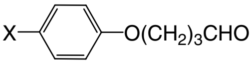
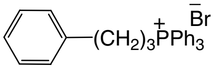
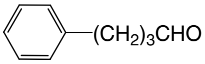
Table 1. Aldehydes produced from Wittig reactions

Entry	Phosphonium salt	Aldehyde product	Yield (%)
			
1	**8**, X = H	**14**, X = H	89
2	**9**, X = Cl	**15**, X = Cl	92
3	**10**, X = OMe	**16**, X = OMe	86
4	**11**, X = CN	**17**, X = CN	83
5	 **12**	 **18**	88
6	$C_{12}H_{25}\overset{+}{P}Ph_3\ \overset{-}{Br}$ **13**	$C_{12}H_{25}CHO$ **19**	95

ketones **2** by a route that avoids the highly reactive organometallic reagents; the conversion is effected upon reaction with alkylidenetriphenylphosphoranes.[6–8]

The preparation of ketones from Weinreb amides parallels the attack of organometallics such as Grignard and organolithium reagents, but we had no parallel route to aldehydes. This letter reports a solution to the task of producing aldehydes using these milder methods.

The Weinreb amide required for the preparation of aldehydes would be *N*-methoxy-*N*-methyl formamide[9] **6** (Scheme 2). Our attempts to prepare it initially foundered. The procedure[9] involves treating the free amine *N*-methoxy-*N*-methylamine **4** with methyl formate **5** in the presence of excess quantities of sodium methoxide. Although the product **6** undoubtedly forms, as seen by NMR, the vacuum distillation needed to purify it led to essentially 0% yield. Our studies showed that the product was converted to volatile compounds; the excess base that was not removed during filtration was reforming methyl formate **5**, via **7**, which was removed in vacuo.

In fact, excess base should not be needed. If catalytic base were to be used and remained at the start of the distillation, this might regenerate small quantities of amine **4** and methyl ester **5**, but these would then disappear from the distillation in vacuo. The amine **4** produced, could not harm the remaining product. In practice, this use of catalytic base led to reliable isolation of the desired product **6**.

This Weinreb amide was then reacted with a series of phosphonium salts (Scheme 3) as shown in Table 1. As seen, the reactions proceeded in excellent yield to afford the corresponding aldehydes after work-up with mild acid.[10] This provides a simple route to aldehydes using a Weinreb amide under mild conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.118.

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