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One-pot synthesis of aldehydes or ketones from carboxylic acids via in situ generation of Weinreb amides using the Deoxo-Fluor reagent

Cyrous O. Kangani,[a,*] David E. Kelley[a] and Billy W. Day[b]

[a]*Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, USA*
[b]*Department of Pharmaceutical Sciences and of Chemistry, University of Pittsburgh, Pittsburgh, PA 15213, USA*

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Abstract—A one-pot, high yield conversion of carboxylic acids to the corresponding aldehydes and ketones is described. The highlight of this methodology is the in situ generation of Weinreb amides with the Deoxo-Fluor reagent, which undergo nucleophilic reaction with DIBAL-H and Grignard reagents.

In recent years, the transformation of carboxylic acids into aldehydes[1] and ketones[2] has received considerable attention because of their significance in synthetic organic chemistry.[3] Extensive efforts have been made toward an efficient synthesis of these functional groups. There are many different synthetic routes to ketones reported in the literature, with the reaction of organometallic reagents with acyl chlorides[4] or Weinreb amides[5] being the most commonly used.

Although the above methods are well documented, the direct addition of Grignard reagents to carboxylic acids to form ketones is an approach that has been largely unsuccessful.[6] To date, ketones are synthesized by multistep synthesis involving derivatization of carboxylic acid into acyl chlorides,[4] Weinreb amides,[5a] thiol esters,[7] imidazolides,[8] and esters,[9] followed by reaction with organometallic reagents. To avoid multi-step syntheses of ketones from carboxylic acid, an efficient one-pot reaction has to be devised.

As part of our program to develop new analytical methods to quantify free fatty acids, we discovered a highly efficient conversion of carboxylic acids to related ketones and aldehydes by a one-pot synthesis using Deoxo-Fluor reagent. Long chain fatty ketones have been detected from a wide variety of sources, for example, insect pheromones, soil waxes, snake skin, and aerosols.[10] Recently it has been shown that fatty ketones may serve as therapeutic agents in the treatment of sleep disorders and pain by targeting fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of the chemical messengers, oleamide and anandamide.[11]

A current practical method for the preparation of ketones involves treatment of acyl chloride with Grignard reagents in the presence of a catalytic amount of metal halide. We decided to employ this procedure, but instead used an acyl fluoride (generated in situ) for conversion to the ketone. Although the desired ketones were obtained by this procedure, the yields and purities were poor. Using the recently reported procedure by Wang et al.,[12] reaction of an in situ generated acyl fluoride and Grignard reagents in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl]ether resulted in a ketone but in extremely low yield[13] (<7% by GC–MS) (Scheme 1).

Weinreb amides are very selective in their reactions with organometallic reagents, giving ketones or aldehydes exclusively in high yields. The efficiency of this process has been attributed to the formation of a stable tetrahedral intermediate even in the presence of excess organometallic reagents.[5a,d] We hypothesized that in situ generated Weinreb amides could be used for direct synthesis of ketones from carboxylic acids via nucleophilic

* Corresponding author. Tel.: +1 412 647 6796; fax: +1 412 692 2165; e-mail: kanganic@msx.dept-med.pitt.edu

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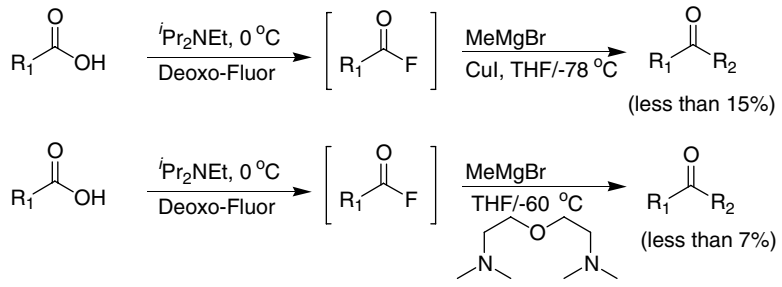
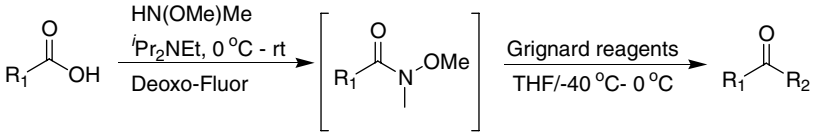


Scheme 1.

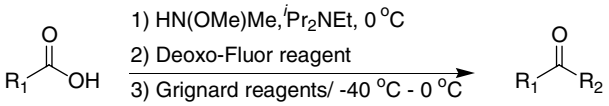


Scheme 2.

reactions of organometallic reagents (Grignard or lithium reagents) (Scheme 2).

Recently, we have demonstrated an efficient method for the one-pot direct synthesis of amides from carboxylic acid.[14] To extend this method to the synthesis of Weinreb amides, we reacted palmitic acid and *N*,*O*-dimethylhydroxyamine at 0 °C with the Deoxo-Fluor reagent.[15] After 15 min at room temperature, TLC examination showed the reaction to be complete. The reaction was quenched with saturated sodium bicarbonate followed by extraction with *n*-heptane and then dried over $MgSO_4$, filtered, and concentrated. GC analysis showed >98% conversion. Delighted by this result, we next examined direct synthesis of ketones from carboxylic acids via in situ generation of Weinreb amides using the Deoxo-Fluor reagent. A mixture of palmitic acid and *N*,*O*-dimethylhydroxyamine in THF/CH_2Cl_2 (5:1) was treated dropwise at 0 °C with the Deoxo-Fluor reagent. After 15 min at room temperature, the reaction mixture (containing the in situ formed Weinreb amide) was cooled to −40 °C and methylmagnesium bromide was added. After stirring the reaction for 2 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and the ketone was isolated in 93% yield. To the best of our knowledge, this is the first example of a one-pot method for the efficient generation of ketones from carboxylic acids. The generality of our method was tested using various carboxylic acids. Aliphatic, aromatic, and unsaturated (cis and trans geometry) carboxylic acids could be converted into the corresponding methyl or phenyl ketones in good to excellent yields. A number of functional groups, including electron withdrawing groups (i.e., nitro), are tolerated under the reaction conditions. In most cases, 6 equiv of the organometallic reagents (Grignard reagents) were found to give the best yields and reaction times. The reaction of phenylmagnesium bromide with various carboxylic acids required more time than did that of methylmagnesium bromide (3 h) to give phenyl ketones (Table 1,

Table 1. One-pot synthesis of ketones from carboxylic acids via in situ generated Weinreb amides

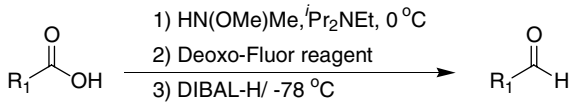


Entry	Carboxylic acid	Grignard reagent (equiv)[a]	Compound number	Yield[b] (%)
1	Palmitic acid	MeMgBr (6)	**1**	92 ± 2, $n = 3$
2	Linoleic acid	MeMgBr (6)	**2**	90 ± 4, $n = 3$
3	Elaidic acid	MeMgBr (6)	**3**	90 ± 2, $n = 3$
4	Benzoic acid	MeMgBr (6)	**4**	90 ± 2, $n = 3$
5	*p*-Toluic acid	MeMgBr (6)	**5**	94 ± 5, $n = 3$
6	*p*-Nitrobenzoic acid	MeMgBr (6)	**6**	92 ± 4, $n = 3$
7	Palmitic acid	PhMgBr (7)	**7**	85 ± 2, $n = 3$
8	Linoleic acid	PhMgBr (7)	**8**	85 ± 2, $n = 3$
9	Elaidic acid	PhMgBr (7)	**9**	80 ± 3, $n = 3$
10	Benzoic acid	PhMgBr (7)	**10**	90 ± 2, $n = 3$
11	*p*-Toluic acid	PhMgBr (7)	**11**	95 ± 3, $n = 3$
12	*p*-Nitrobenzoic acid	PhMgBr (7)	**12**	86 ± 5, $n = 3$

[a] Equivalents of Grignard reagent relative to carboxylic acid.

[b] Refers to isolated yield of purified product ± SD. The purity of all products was determined to be 97–99% by ^1H and ^{13}C NMR spectroscopy and GC–MS analysis.

Table 2. One-pot synthesis of aldehydes from carboxylic acids via in situ generation of Weinreb amides



Entry	Carboxylic acid	Compound number	Yield[a] (%)
1	Palmitic acid	**13**	83
2	Linoleic acid	**14**	79
3	Elaidic acid	**15**	73
4	Benzoic acid	**16**	90
5	*p*-Toluic acid	**17**	86
6	*p*-Nitrobenzoic acid	**18**	91

[a] Yield of pure isolated products, characterized by GC–MS, ^{1}H NMR, and ^{13}C NMR.

entries 6–12). The reaction of unsaturated carboxylic acids (linoleic acid and elaidic acid) with methylmagnesium bromide as well as phenylmagnesium bromide gave the corresponding ketones in very good yields (Table 1, entries 2, 3, 8, and 9).

Given the encouraging results, we next examined conversion of carboxylic acids into the corresponding aldehydes. Reduction of in situ formed Weinreb amide with DIBAL-H generated the aldehyde in very good yield. The Deoxo-Fluor reagent was added dropwise to a mixture of palmitic acid and *N*,*O*-dimethylhydroxyamine at 0 °C, stirred for 15 min at room temperature (resulting in formation of the Weinreb amide) and then cooled to −78 °C, followed by dropwise addition of DIBAL-H (7 equiv). After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and the aldehyde was isolated in 83% yield (Table 2, entry 1). Other representative results are listed in Table 2. The reaction worked very well with both aliphatic and aromatic carboxylic acids.

In conclusion, we have developed an operationally simple, one-pot, two-step method for the synthesis of aldehydes and ketones by addition of, DIBAL-H and Grignard reagents, respectively, to in situ generated Weinreb amides. The notable advantages of this procedure are its (a) operational simplicity, (b) general applicability to aromatic and aliphatic (both saturated and unsaturated) carboxylic acids, (c) reaction conditions that are tolerant to a variety of sensitive functional groups, (d) elimination of the need to isolate the intermediate, and (e) high yields. We believe that this protocol provides a practical alternative to the existing methods available for the synthesis of aldehydes and ketones from their corresponding carboxylic acids.

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Supplementary data

A description of the general methods used to prepare, and spectroscopic data (^{1}H and ^{13}C NMR) for all products are given in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.121.

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