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Direct Conversion of *N*-Methoxy-*N*-methylamides (Weinreb Amides) to Ketones via a Nonclassical Wittig Reaction

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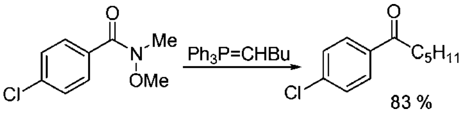
ABSTRACT



***N*-Methoxy-*N*-methylamides (Weinreb amides) are converted efficiently into ketones by reaction with alkylidenetriphenylphosphoranes and in situ hydrolysis of the product.**

The efficient manipulation of the carbonyl functional group is of pivotal importance in synthetic chemistry and crucial for the successful and efficient preparation of synthetic targets of varying complexity. An important and widely used transformation has proven to be the direct conversion of carbonyl compounds, at the carboxyl oxidation level, directly to the corresponding aldehydes and ketones. The development of *N*-methoxy-*N*-methylamides as carboxylate synthons[1] has admirably fulfilled this role, allowing the direct preparation of highly functionalized aldehydes and ketones upon reaction with appropriate organometallic nucleophiles.[2] The efficiency of this process has been attributed to the intermediacy of an exceptionally stable tetrahedral chelate,[2] which retards secondary addition of the nucleophile. The stability of the chelate has itself found elegant application in synthetic protocols,[3] providing aldehydes and ketones in latent form, allowing a second transformation to be performed chemoselectively in its presence.

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(1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(2) Recent representative examples include: (a) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855. (b) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (c) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2000**, *2*, 4041. (d) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145 (e) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, 122, 8654. (f) Trost, B. M.; Gunzner, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 9449. (g) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973. (h) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307. (i) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263. (j) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. (k) Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958. (l) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 9328. (m) Cheung, A. K.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 11584. (n) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (o) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196. (p) Toda, N.; Ori, M.; Takami, K.; Tago, K.; Kogen, H. *Org. Lett.* **2003**, *5*, 269. (q) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H, -X.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. (r) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041. (s) Taillier, C.; Bellosta, V.; Cossy, J. *Org. Lett.* **2004**, *6*, 2145. (t) Taillier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2149. (u) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704.

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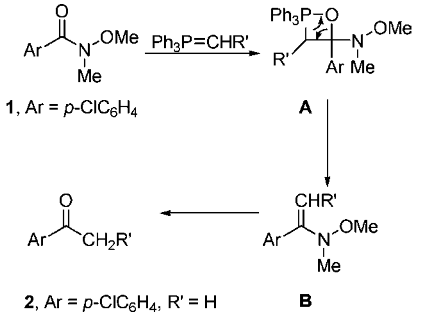
Although the transformation is extremely useful, the reactivity of the organometallic reagents that react with Weinreb amides must be taken into account when planning synthetic transformations. Reagents such as DIBAL-H, LiAlH$_4$, Grignard and organolithium reagents are incompatible with a number of functional groups. It would be a significant advance if less aggressive conditions could be found for effecting the same transformations. 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.

We now report a highly efficient conversion of *N*-methoxy-*N*-methylamides to related ketones by a route that avoids the highly reactive organometallic reagents; the conversion is effected upon reaction with alkylidenetriphenylphosphoranes (Scheme 1). The reaction is particularly surprising in view of the completely different reaction of phosphonate anions with Weinreb amides. Thus, it is well-known[2g,k] that phosphonate anion reacts with Weinreb amides **3** to form β-ketophosphonates **4**, a completely different outcome from that seen in our reactions (Scheme 2).

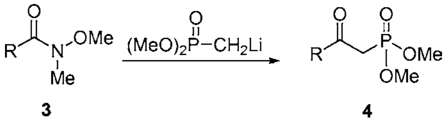
Scheme 1



1, Ar = *p*-ClC$_6$H$_4$

2, Ar = *p*-ClC$_6$H$_4$, R' = H

Scheme 2



3

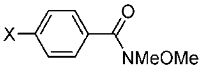
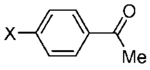
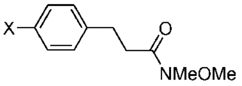
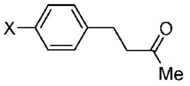
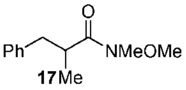
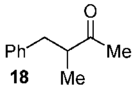
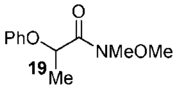
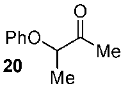
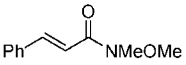
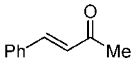
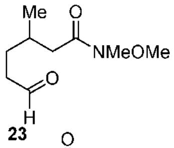
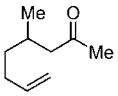
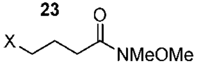
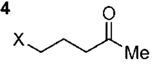
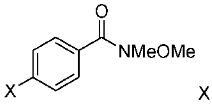
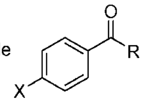
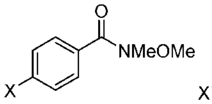
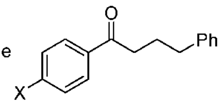
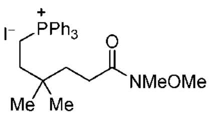
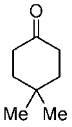
4

We propose a nonclassical Wittig reaction[6] to account for our observed product. Taking **1** as an example, reaction of *N*-methoxy-*N*-methylamides would form oxaphosphetane **A**, which upon cycloreversion extrudes triphenylphosphine oxide affording putative enamine **B**. Mild hydrolysis of **B** would then give rise to methyl ketone **2**.

Preliminary studies carried out on 1-chlorobenzyl-4-(*N*-methoxy-*N*-methylamide) (**1**) under a variety of Wittig conditions indicated that best yields of 4-chloroacetophenone (**2**) were obtained when methylenetriphenylphosphorane (2.1 equiv), generated with *n*-BuLi, was allowed to react with **1** in THF.

To provide corroboratory evidence for such a pathway, we worked up the product from reaction of Weinreb amide **5**, with a D$_2$O and catalytic H$_2$SO$_4$ quench, followed by

Table 1. Reactions of Weinreb Amides with Phosphoranes

entry	weinreb amide	product	yield
			
1	**1**, X = Cl	**2**, X = Cl	91 %
2	**5**, X = F	**7**, X = F	83 %
3	**9**, X = H	**10**, X = H	72 %
4	**11**, X = CN	**12**, X = CN	75 %
			
5	**13**, X = H	**14**, X = H	55 %
6	**15**, X = OMe	**16**, X = OMe	79 %
7	 **17**	 **18**	75 %
8	 **19**	 **20**	69 %
9	 **21**	 **22**	50 %
10	 **23**	 **24**	42 %
			
11	**25**, X = CH$_2$Br	**26**, X = CH$_2$Br	63%
12	**27**, X = CH$_2$Cl	**28**, X = CH$_2$Cl	68%
13	**29**, X = Cl	**30**, X = Cl	51%
			
14	**1**, X = Cl	**31**, X = Cl, R = C$_5$H$_{11}$	83 %
15	**1**, X = Cl	**32**, X = Cl, R = C$_4$H$_9$	89 %
16	**5**, X = F	**33**, X = F, R = C$_4$H$_9$	78 %
17	**9**, X = H	**34**, X = H, R = C$_4$H$_9$	83 %
			
18	**1**, X = Cl	**35**, X = Cl	76 %
19	**5**, X = F	**36**, X = F	77 %
20	**9**, X = H	**37**, X = H	67 %
21	 **38**	 **39**	51 %

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(3) For representative examples, see: (a) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

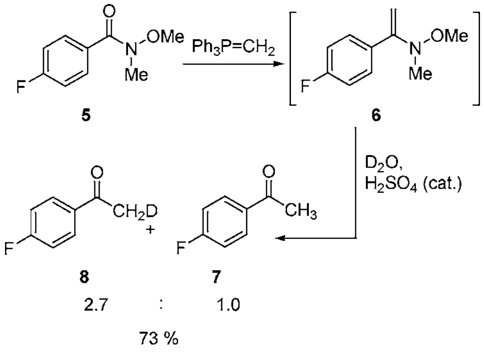
(4) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.

(5) Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M.; Stessman, C.; Oien, L. *Tetrahedron Lett.* **1995**, *36*, 6209.

(6) (a) Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1. (b) Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049.

normal workup procedures, affording a mixture of **8** and **7** in a 2.7:1 ratio (determined by ^{1}H NMR) (Scheme 3). No evidence of polydeuteration was observed that would arise from exchange between **7** and D_2O under acidic conditions, thus providing viable evidence for the existence of **B**.

Scheme 3



The scope of the reaction was then tested (Table 1).

Entries 7 and 8 show that the reaction succeeds well with α-branched Weinreb amides, although attempts to convert the amide of pivalic acid (not shown) have not yet proved successful. The reaction works well with aromatic Weinreb amides (entries 1−4, 14−20), α,*β*-unsubstituted examples (entry 9), and also with α-heterosubstitution (entry 8). Dual transformation can be achieved with aldehyde−amide substrates (entry 10). The reaction is also chemoselective, where a nitrile group (entry 4) and aliphatic halides (chloride, bromide) (entries 11−13) do not interfere with the reaction.

The reaction is not limited to methylenetriphenylphosphorane, with pentylenetriphenylphosphorane (entry 14), butylenetriphenylphosphorane (entries 15−17), and 3-phenylpropylenetriphenylphosphorane (entries 18−20) also giving excellent results. Also worthy of note is the successful application of this reaction in an intramolecular fashion affording 4,4-dimethylcyclohexanone (51%, entry 21) upon treatment of the precursor phosphonium iodide with KHMDS in THF.

Wittig reactions on amides are known;[7] however, these systems are usually subject to severe perturbation, in a conformational or electronic sense, limiting resonance contribution from the nitrogen lone pair. We speculate that the inductive effect from the oxygen of the *N*-OMe group locally perturbs this system, thus permitting reactivity in the manner described.

In conclusion, a new transformation of Weinreb amides is announced that permits the efficient synthesis of related ketones. The conditions of this reaction are much milder than the conventional route using organometallic reagents. Its chemoselectivity is particularly seen in the clean transformations of cyano- or halo-substituted substrates.

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Supporting Information Available: Typical experimental procedures for the reactions of Weinreb amides are provided together with spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] For intermolecular examples, see: (a) Bohlmann, R.; Strehlke, P. *Tetrahedron Lett.* **1996**, *37*, 7249. (b) Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785. (c) Bégué, J.-P.; Mesureur, D. *Synthesis* **1989**, 309. (d) Prasitpan, N.; Patel, J. N.; De Croos, P. Z.; Stockwell, B. L.; Manavalan, P.; Kar, L.; Johnson, M. E.; Currie, B. L. *J. Heterocycl. Chem.* **1992**, *29*, 335. For intramolecular examples, see: (e) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313. (f) Li, J. P.; Newlander, K. A.; Yellin, T. O. *Synthesis* **1988**, 73. (g) Eitel, M.; Pindur, U. *Synthesis* **1989**, 364. (h) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Silvani, A. *Tetrahedron* **1994**, *50*, 6941. (i) Coulton, S.; Gilchrist, T. L.; Graham, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1193.