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A Powerful Reagent for Synthesis of Weinreb Amides Directly from Carboxylic Acids

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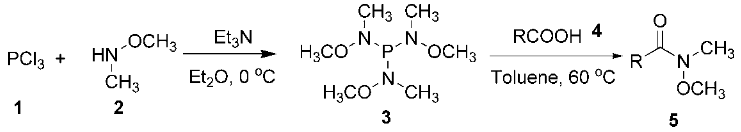
ABSTRACT



A powerful reagent, $P[NCH_3(OCH_3)]_3$ (3), for conversion of carboxylic acids directly to Weinreb amides was developed. In most cases the yields of the corresponding Weinreb amides were above 90% when $P[NCH_3(OCH_3)]_3$ was heated with aromatic and aliphatic carboxylic acids in toluene. The sterically hindered carboxylic acids can also give the corresponding Weinreb amides in excellent yields.

Weinreb amides (*N*-methoxy-*N*-methylamides) have been developed into important and effective acylating agents since their original discovery by Nahm and Weinreb in 1981.[1−4] They could cleanly react with Grignard reagents,[5,6] organolithium,[7,8] and $LiAlH_4$[3] to give ketones or aldehydes in high yield via stable metal-chelated intermediates without dual nucleophilic attack to their carbonyl group even with excess of organometallic reagents. Rencently, it was also reported that they could react with Wittig reagents to give ketones.[9] Because of their effectiveness as acylating reagents, Weinreb amides have now been widely used in total synthesis of natural products .[10−15]

Significant effort has been devoted toward the development of their mild and general synthesis in recent years. For example, Weinreb amides can be prepared via carboxylic acids,[16−18] acid chlorides,[1,19] esters,[20] lactones,[21] amides,[22] and anhydrides.[23] Among them the direct conversion of carboxylic acids to the corresponding Weinreb amides is very attractive. Peptide coupling reagents such as BOP,[24,25]

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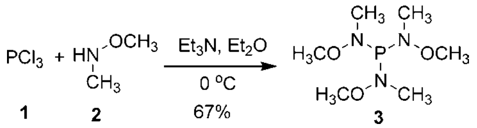
DCC,[26] chloroformates,[27] phosphonic derivatives,[28−30] 2-chloro-1-methylpyridinium iodide (CMPI),[31] BMPI,[32] Deoxo-Fluor, and triazine derivatives[33] have been applied for this transformation.

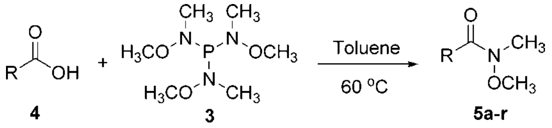
Several other methods for the preparation of Weinreb amides have been reported, which include Stille-type cross-coupling,[34] Pd-catalyzed aminocarbonylation of aryl bromides,[35] and heterocyclic-derived triflates.[36] Sterically hindered Weinreb amides were also successfully obtained from carboxylic acids via mixed anhydrides with methanesulfonic acid.[37] In addition, synthesis of α-siloxy-Weinreb amides from aldehydes has been reported.[38] However, the use of an excess of expensive coupling reagents is necessary in most of these methods, and the sterically hindered carboxylic acids often give the corresponding Weinreb amides in poor yields. Thus, the development of general and efficient methods for synthesis of Weinreb amides is still highly desirable.

Attracted by wide application of Weinreb amides in natural product synthesis, we intended to explore a simple and practical method to synthesize Weinreb amides. In the literature, we found that $P(NMe_2)_3$ could convert carboxylic acids to the corresponding amides in high yields.[39] We envisioned that $P[NCH_3(OCH_3)]_3$ would be able to react with carboxylic acids to afford Weinreb amides. Thus, we prepared $P[NCH_3(OCH_3)]_3$ from PCl_3 and $HNCH_3(OCH_3)$ (Scheme 1) and then heated it with carboxylic acids in toluene (Scheme 2). To our delight, Weinreb amides were obtained in excellent yields. In this paper, we report that $P[NCH_3(OCH_3)]_3$ could convert carboxylic acids directly to Weinreb amides in excellent yields under mild conditions.

Scheme 1. Synthesis of $P[NCH_3(OCH_3)]_3$



Scheme 2. Synthesis of Weinreb Amides from Compound **3** and Carboxylic Acids



We first treated PCl_3 with *N*,*O*-dimethylhydroxylamine hydrochloride in Et_2O using triethylamine as base to give compound **3** in 67% yield (Scheme 1). Although compound **3** was obtained, the yield was not so good. In order to improve the yield of compound **3**, excess *N*,*O*-dimethylhydroxylamine was used in a subsequent reaction without using triethylamine as base for trapping of HCl released from the reaction. However, the yield of **3** was 70%, which is almost the same as the yield in using Et_3N as base. Thus, triethylamine was an effective base for trapping of the HCl. We used triethylamine as base in our experiment because it was much cheaper than *N*,*O*-dimethylhydroxylamine.

With $P[NCH_3(OCH_3)]_3$ in hand, we initially examined the reaction of **3** with benzoic acid. Benzoic acid and $P[NCH_3(OCH_3)]_3$ were heated at 80 °C for 1 h in toluene, and the corresponding Weinreb amide was obtained in 79% yield (Table 1, entry 1). The reaction conditions were optimized using benzoic acid as substrate (Table 1).

As can be seen in Table 1, the mole ratio of benzoic acid and **3** had a great effect on the yield of product. The ratio of benzoic acid to **3** should be 3:1 theoretically. However, it was found that the reaction gave the best result with 95% yield of product when the mole ratio of benzoic acid and $P[NCH_3(OCH_3)]_3$ is 2:1 (Table 1, entry 3). It was observed that the reaction temperature had no significiant influence on the yield of **5a** (Table 1, entries 4−7). When the

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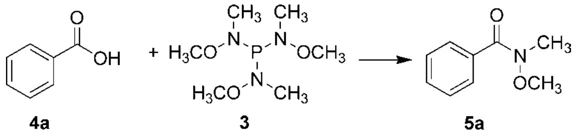
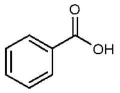
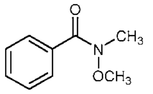
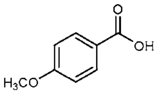
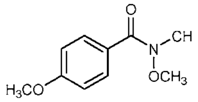
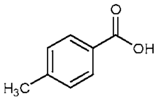
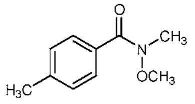
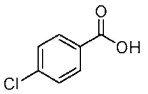
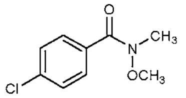
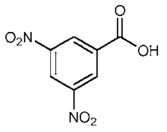
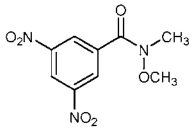
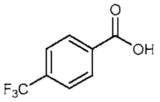
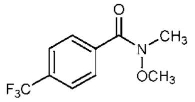
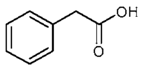
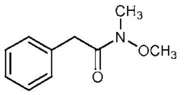
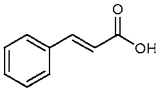
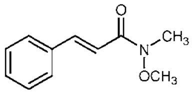
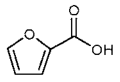
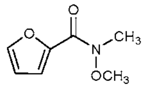
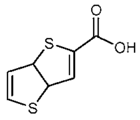
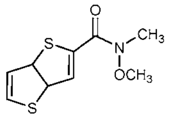
Table 1. Optimization of Reaction Conditions for Synthesis of Weinreb Amides



entry	**4a** (mmol)	**3** (mmol)	time (h)	*T* (°C)	solvent	yield[a] (%)
1	3.0	1	1	80	toluene	79
2	2.5	1	1	80	toluene	86
3	2.0	1	1	80	toluene	95
4	2.0	1	1	60	toluene	94
5	2.0	1	0.5	60	toluene	93
6	2.0	1	0.5	40	toluene	89
7	2.0	1	1	40	toluene	93
8	2.0	1	2	20	toluene	87
9	2.0	1	2	20	CH_2Cl_2	60
10	2.0	1	2	20	Et_2O	55
11	2.0	1	6	20	CH_2Cl_2	88
12	2.0	1	6	20	Et_2O	78

[a] Isolated yield.

Table 2. Synthesis of Weinreb Amides from Compound **3** and Aromatic Carboxylic Acids[a]

entry	substrate	product		yield (%)[b]
1	 **4a**		**5a**	94
2	 **4b**		**5b**	92
3	 **4c**		**5c**	95
4	 **4d**		**5d**	96
5	 **4e**		**5e**	95
6	 **4f**		**5f**	89
7	 **4g**		**5g**	95
8	 **4h**		**5h**	95
9	 **4i**		**5i**	96
10	 **4j**		**5j**	95

[a] Reaction conditions: **3** (1 mmol) and carboxylic acid (2 mmol) in toluene (10 mL) at 60 °C for 0.5−1 h. [b] Isolated yield.

temperature was above 60 °C, an excellent yield of Weinreb amide could be obtained in 0.5 h (Table 1, entry 5). However, even if the reaction was conducted at 20 °C, a good result could also be obtained with a longer reaction time (Table 1, entry 8).

We have also investigated the effects of solvents on the reaction. CH_2Cl_2 or Et_2O was used as solvent. It was found that the reaction could also occur in CH_2Cl_2 or Et_2O, but the yield was lower than that in toluene (Table 1, entries 8−10). If the reaction was carried out in CH_2Cl_2 or Et_2O for a suitable amount of time, the yield of the product was also satisfactory (Table 1, entries 11 and 12).

In order to examine the effectiveness of the reagent **3**, different kinds of carboxylic acids were subjected to the optimized set of conditions (Tables 2 and 3).

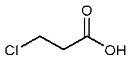
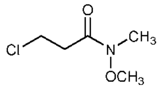
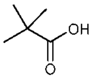
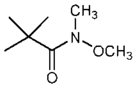
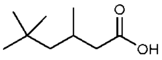
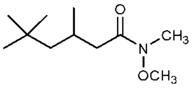
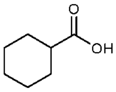
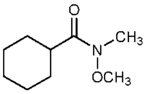
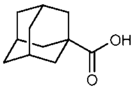
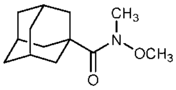
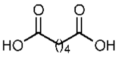
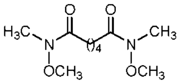
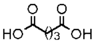
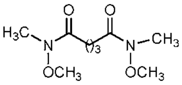
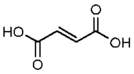
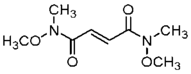
Table 2 shows the results with aromatic carboxylic acids. As can be seen in Table 2, all of the aromatic carboxylic acids with electron-withdrawing or electron-donating groups on their phenyl ring could be converted to the corresponding Weinreb amides in yields above 90%. Benzyl and heteroaromatic acids gave products in 95−96% yields (Table 2, entries 7−10).

The results for conversion of aliphatic acids to the corresponding Weinreb amides are shown in Table 3. All of the used aliphatic carboxylic acids gave the products in excellent yields. Halide group such as chlorine in aliphatic acids could be present. For example, when 3-chloropropanoic acid was used as substrate, 3-chloro-*N*-methoxy-*N*-methylpropanamide **5k** was obtained in 92% yield (Table 3, entry 1). Dioic acids also smoothly reacted with compound **3** to give the bis-Weinreb amides in high yields (Table 3, entries 6−8).

Most importantly, compound **3** could also convert sterically hindered carboxylic acids to the corresponding Weinreb amides in excellent yields. For example, the reaction of **3** with pivalic acid **4l** and adamantane-1-carboxylic acid **4o** gave the products in 83% and 91% yield, respectively (Table 3, entries 2 and 5). It was found that when *trans*-2-butenedioic acid **4r** reacted with compound **3**, the corresponding product was formed in 89% yield with retention of configuration (Table 3, entry 8).

However, as shown in Scheme 3, when the reaction was carried out with *cis*-2-butenedioic acid **4s** at 60 °C in toluene for 2 h, the correspoding *cis*-product **5s** with retention of configuration was formed only in 47% yield, and the *trans*-product **5r** with change of configuration was formed in 42%

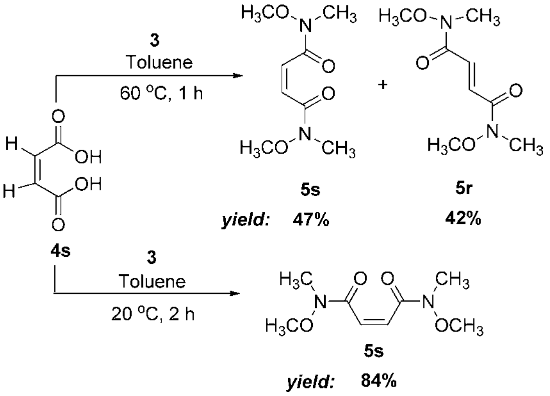
Table 3. Synthesis of Weinreb Amides from Compound **3** and Aliphatic Carboxylic Acids[a]

entry	substrate	product		yield (%)[b]
1	 **4k**		**5k**	92
2	 **4l**		**5l**	83
3	 **4m**		**5m**	92
4	 **4n**		**5n**	95
5	 **4o**		**5o**	91
6	 **4p**		**5p**	89[c]
7	 **4q**		**5q**	86[c]
8	 **4r**		**5r**	89[c]

[a] Reaction conditions: **3** (1 mmol) and carboxylic acid (2 mmol) in toluene (10 mL) at 60 °C for 0.5−1 h. [b] Isolated yield. [c] **3** (1 mmol) and carboxylic acid (1 mmol).

yield. If the reaction was carried out at a lower temperature such as 20 °C in toluene for 2 h, there was no change of the configuration, and the yield of the product **5s** was 84%.

Scheme 3. Reaction of Compound **3** and Maleic Acid



Another advantage of compound **3** is that it can be prepared and used on a large scale without a big difference on a small scale.

In summary, we have developed a highly effective reagent **3** for the formation of Weinreb amides directly from carboxlic acids. Compound **3** could be easily prepared from PCl_3 and *N*,*O*-dimethylhydroxylamine hydrochloride in Et_2O. It can be applied to the transformation of different kinds of carboxylic acids such as aromatic, aliphatic, sterically hindered, and dioic acids into the corresponding Weinreb amides in excellent yields under very mild conditions.

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Supporting Information Available: Typical experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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