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A Convenient Method for the Conversion of Hindered Carboxylic Acids to *N*-Methoxy-*N*-methyl (Weinreb) Amides

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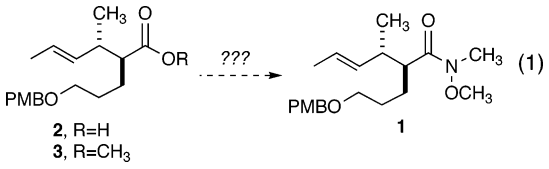
Abstract: The conversion of sterically hindered carboxylic acids to *N*-methoxy-*N*-methyl amides can be efficiently carried out with 1.1 equiv of methanesulfonyl chloride, 3 equiv of triethylamine, and 1.1 equiv of *N*-methoxy-*N*-methylamine. Yields for this process range from 59% to 88%. The major byproduct in these reactions, *N*-methoxy-*N*-methylmethanesulfonamide, can be removed by placing the product mixture under vacuum for 14−24 h.

Since their initial appearance in 1981, *N*-methoxy-*N*-methyl (Weinreb) amides have proven to be important acylating reagents in organic chemistry.[1] The predictable reactivity and effectiveness of Weinreb amides have ensured their use as intermediates within many complex total synthesis ventures.[2] In the context of a total synthesis project ongoing in our research laboratory,[3] we had a need to generate Weinreb amide **1** from carboxylic acid **2** (or its corresponding methyl ester **3**) (eq 1). Given the relative simplicity of carboxylic acid **2**, we were surprised to discover that several literature procedures for the construction of Weinreb amides gave disappointing results (eq 2 and Table 1).[1a,4] This seemingly trivial transformation to produce **1** was plagued with poor isolated yields or low conversions.



We speculated that steric encumbrance around the carboxyl group was the source of this problem. The Nicolaou group had published a method for the formation of hindered α-diazoketones that was presumed to proceed through a mixed anhydride of methanesulfonic acid (an acyl mesylate).[5] As this procedure appeared to be an effective method for activating hindered carboxylic acids, we subjected **2** (on a 50 mg scale) to the original conditions of 5 equiv of distilled methanesulfonyl chloride and 10 equiv of triethylamine followed by 10 equiv of *N*,*O*-dimethylhydroxylamine (eq 3).[6] To our delight, the

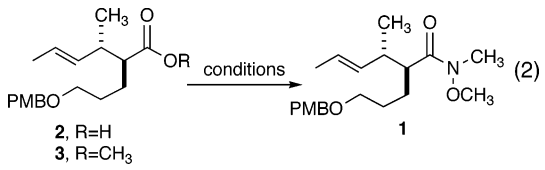


TABLE 1. Initial Attempts to Convert 2 or 3 to 1

entry	starting material	conditions	*T* (°C)	*t* (h)	yield of **1** (%)[a]
1	**2**	(MeO)MeNH, DCC, HOBt, NEt_3	0−rt	14	21[b]
2	**2**	(MeO)MeNH, EDC, HOBt, NEt_3	0−rt	14	38[b]
3	**2**	(MeO)MeNH, PyBOP, DIEA	rt	14	21[b]
4	**2**	(MeO)$MeNH_2Cl$, C_5H_5N, CBr_4, PPh_3	rt	0.5	30[b]
5	**3**	(MeO)MeNH·HCl, $Al(CH_3)_3$	−15−rt	2	NR
6	**3**	(MeO)MeNH·HCl, $Al(CH_3)_3$	45	15	complex
7	**3**	(MeO)MeNH·HCl, *i*PrMgCl	−20	2	NR
8	**3**	(MeO)MeNH·HCl, *i*PrMgCl	65	15	complex

[a] NR = no reaction; complex = complex mixture. No desired amide was observed in the product mixture by chromatography. [b] Unreacted starting material was also obtained.

(1) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. For reviews, see: (b) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967−993. (c) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340−347. (d) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517−524. (e) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15−40.

(2) Some recent examples: (a) Perez, M.; del Pozo, C.; Reyes, F.; Rodriguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1724−1727. (b) Mulzer, J.; Berger, M. *J. Org. Chem.* **2004**, *69*, 891−898. (c) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041−1044. (d) Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. Z. *Org. Lett.* **2003**, *5*, 925−927. (e) Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899−10905. (f) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393−5407.

(3) Wilson, M. S.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2041−2044.

(4) DCC coupling: (a) Gibson, C. L.; Handa, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1281−1284. PyBop coupling: (b) D'Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870−4871. *i*PrMgCl and amine salt: (c) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

(5) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Choi, H. S.; Fong, K. C.; He, Y.; Yoon, W. H. *Org. Lett.* **1999**, *1*, 883−886. (b) Nangia, A.; Chandrasekaran, S. *J. Chem. Res. S* **1984**, 100. (c) Jacobi, P. A.; Sessions, E. H. *Synth. Commun.* **2003**, *33*, 2575−2579. (d) Chandrasekaran, S.; Turner, J. V. *Synth. Commun.* **1982**, *12*, 727−731. For the use of *p*-TsCl and *N*-methylimidazole for simple esterification, thioesterification, and amidation, see: (e) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345* (11), 1209−1214.

(6) For other recently disclosed methods for the formation of Weinreb and related amides, see: (a) White, J. M.; Tunoori, A. R.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2004**, *69*, 2573−2576 (deoxo-fluor reagant). (b) Hioki, K.; Kobayashi, H.; Ohkihara, R.; Tani, S.; Kunishima, M. *Chem. Pharm. Bull.* **2004**, *52*, 470−472 (DMT-MM). (c) Katritzky A. R.; Kirichenko, N.; Rogovoy, B. V. *Synthesis* **2003**, 2777−2780 (acylbenzotriazole intermediate). (d) Kim, M.; Lee, H.; Han, K. J.; Kay, K. Y. *Synth. Commun.* **2003**, *33*, 4013−4018 (trichloromethylchloroformate). (e) Sibi, M. P.; Hasegawa, H.; Ghorpade, S. R. *Org. Lett.* **2002**, *4*, 3343−3346 (oxazolidinone with amine and lanthanide triflate). (f) Banwell, M.; Smith, J. *Synth. Commun.* **2001**, *31*, 2011−2019 (Mukaiyama amide coupling). (g) Huang, P. Q.; Zheng, X.; Deng, X. M. *Tetrahedron Lett.* **2001**, *42*, 9039−9041 (DIBAL-H·amine complexes). (h) Bailen, M. A.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. *Tetrahedron Lett.* **2001**, *42*, 5013−5016 (thiouronium salts). (i) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534−2537 (CDMT and NMM). (j) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091−4093 (deoxo-fluor). (k) Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. *Synth. Commun.* **1999**, *29*, 3215−3219 (pivaloyl chloride). (l) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685−2688 (Me_2AlCl·amine complex).

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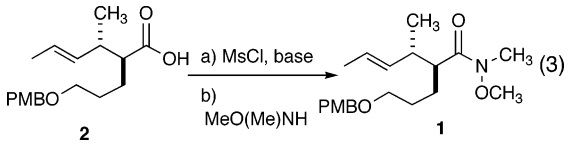


desired Weinreb amide **1** was formed in 80% isolated yield. Unfortunately, the yield of **1** significantly dropped to 55% due to byproduct formation (deprotection of the *p*-methoxybenzyl group) when this reaction was scaled to 1 g of **2** or larger. Subsequent modification of the reaction parameters resulted in an optimized procedure using 1.1 equiv of methanesulfonyl chloride, 3 equiv of triethylamine, and 1.5 equiv of *N*,*O*-dimethylhydroxylamine in THF at 0 °C to produce **1** in 80% yield on a 1 g scale. That this procedure succeeded where other processes had failed was quite satisfying. Indeed, further attempts to produce **1** with alternative conditions ($SOCl_2$, C_5H_5N, (MeO)MeNH or $^tBuCO_2Cl$, Et_3N, (MeO)MeNH·HCl) resulted in its formation in only 54% and 55% yields, respectively.

A number of other hindered acids were subjected to the optimized set of conditions to examine the effectiveness of this procedure (eq 4 and Table 2).[7] Simple, unhindered carboxylic acids (e.g., butanoic acid) were not examined because of the efficiency of previously established procedures. As can be seen in the table, a number of hindered acids are smoothly converted to their corresponding Weinreb amides in reasonable yields (59−88%).[8,9] The reaction proceeds smoothly on aromatic (entries 1 and 7) and aliphatic systems. Importantly, the reaction conditions are mild enough such that epimerization of stereogenic carbon centers adjacent to the carbonyl carbon do not occur (eq 3 and Table 2, entries 11 and 12). The mildness of this procedure compared to the reagent combination of trimethylaluminum and *N*,*O*-dimethylhydroxylamine hydrochloride bodes well for its use in "large scale" applications (multiples of grams) in an academic setting.

Although the reaction proceeds smoothly, it can be complicated by the formation of *N*-methoxy-*N*-methylmethanesulfonamide as a byproduct. The removal of this contaminant with standard chromatography manipulations can be tricky as it is difficult to visualize on thin-layer chromatographs. The most successful approach to removing this byproduct is gently warming the contaminated Weinreb amide under vacuum overnight. In most cases this protocol can remove the majority of the undesired byproduct, allowing for the isolation of the desired amide in >98% purity by NMR spectroscopy.

In summary, a method useful for the formation of *N*-methoxy-*N*-methylamides from sterically hindered carboxylic acids has been described. This procedure putatively involves the formation of a mixed anhydride of methanesulfonic acid (an "acyl mesylate"). This procedure was invaluable in solving our particular synthetic problem, and thus it may prove useful for other practitioners of organic chemistry.

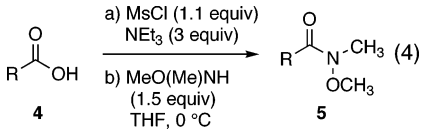
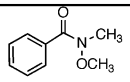
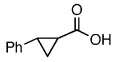
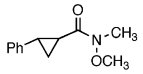
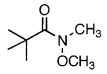
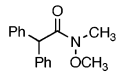
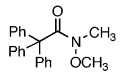
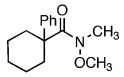
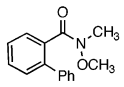
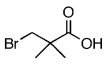
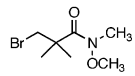
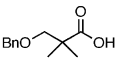
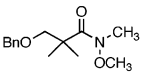
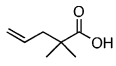
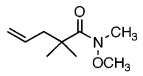
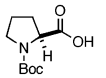
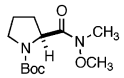
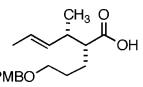
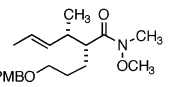


TABLE 2. Formation of Hindered Weinreb Amides[a]

entry	series	starting material	product	yield (%)
1	**a**			61
2	**b**			61
3	**c**			71
4	**d**			64
5	**e**			77
6	**f**			88
7	**g**			68
8	**h**			59
9	**i**			85
10	**j**			84
11	**k**			76
12	**l**			84

[a] Reactions were performed with 1.1 equiv of MsCl, 3 equiv of NEt_3, and 1.5 equiv of Me(MeO)NH. [b] Isolated yields.

Experimental Section

Sample Experimental Procedure. *N*,*O*-Dimethylhydroxylamine was prepared from its commercially available hydrochloride salt.[10] A 250-mL round-bottom flask was charged with 24.3 g of *N*,*O*-dimethylhydroxylamine hydrochloride (250 mmol), 100 mL of ethylene glycol, and 41 mL of triethanolamine (310 mmol). A short-path distillation head was affixed to the flask and the thick slurry heated to reflux to collect the free amine (bp 47−50 °C).

(7) Carboxylic acids **4a**−**g**,**j**,**k** are commercially available. Carboxylic acids **4h** and **4i** can be prepared from 2,2-dimethyl-1,3-propanediol with straightforward methods. Carboxylic acids **2** and **4l** are products resulting from an Ireland−Claisen rearrangement: Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1981**, *56*, 650−657.

(8) Some of these amides have been previously prepared: **5a**, **5c**, **5d**, **5k**: see ref 6f. **5b**: Rodriques, K. E. *Tetrahedron Lett.* **1991**, *32*, 1275−1278. All previously unreported amides have been fully characterized (IR, ^1H, ^{13}C NMR). Please refer to the Supporting Information.

(9) It was not rigorously established whether the reaction proceeds through the intermediacy of an acyl mesylate, an acid chloride, or an anhydride. Each is a conceivable intermediate.

(10) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054−11080.

To a solution of 7.33 g of acid **2** (23.92 mmol) in 240 mL of THF at 0 °C was added 10.0 mL of triethylamine (71.77 mmol), then 2.04 mL of freshly distilled methanesulfonyl chloride (26.31 mmol) was added dropwise. The reaction was stirred at 0 °C for 10 min, and salt formation was observed. To the suspension was added 2.64 mL of *N,O*-dimethylhydroxylamine (35.88 mmol) and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with 120 mL of H_2O and diluted with 120 mL of Et_2O. The separated aqueous layer was extracted with 3 × 120 mL of Et_2O. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (1/1 petroleum ether−ether) afforded 6.7 g (80%) of a colorless oil.

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Supporting Information Available: Experimental procedures and characterization data for previously unreported *N*-methoxy-*N*-methylamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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