An Easy and Convenient Synthesis of Weinreb Amides and Hydroxamates

Lidia De Luca, Giampaolo Giacomelli,* and Maurizio Taddei

Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2, I-07100 Sassari, Italy

ggp@ssmain.uniss.it

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The so-called Weinreb amides[1] (or *N*-methoxy-*N*-methyl amides) are versatile building blocks in organic synthesis.[2] Their preparation can be accomplished by coupling carboxylic acids and *N*,*O*-dimethylhydroxylamine. The majority of the methods reported uses peptide coupling reagents such as chloroformates,[3] BOP,[4] DCC,[5] and others[6] or phosphonic derivatives.[7] These reactives are expensive in some cases, and the removal of their excess (and/or the removal of byproducts) from the reaction mixtures may be difficult. Additional purification of the reaction product is often required. The importance of Weinreb amides is attested by a recent communication describing a one-flask synthesis of Weinreb amides of carboxylic and amino acids using a Deoxo-Fluor fluorinating reagent.[8] Although simple, this method requires the use of an expensive reagent. Moreover, the crude products must be separated by column chromatography.

Following our interest in the use of [1,3,5]triazine derivatives in organic synthesis,[9] we report here a new simple and high-yielding one-flask synthesis of Weinreb amides from carboxylic acids and *N*-protected amino acids that uses different [1,3,5]triazine derivatives as the coupling agents. The method allows the preparation of Weinreb amides and hydroxamates as *O*-benzyl and *O*-silyl hydroxamates[10] that can be easily transformed into hydroxamic acids.

Treating a carboxylic acid with 2-chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT) and *N*-methylmorpholine (NMM) in THF, the corresponding activated ester is quantitatively formed in 1 h (monitored by TLC). This white suspension, containing the activated ester, is subsequently treated with the required hydroxylamine derivative (*N*,*O*-dimethylhydroxylamine for the Weinreb amide and *O*-benzyl- or *tert*-butyldiphenylsilyl hydroxylamine[11] for hydroxamates). Stirring is continued for 8 h at room temperature. The reaction mixture is diluted with ether and then washed with water, aqueous Na_2CO_3, diluted HCl, and brine. The desired product is recovered in pure form, simply by concentration of the ether extracts at reduced pressure.

As shown in Table 1, a variety of *N*-methoxy-*N*-methyl amides were prepared from commercially available carboxylic acids and amino acids (method A). In all cases, the yields were quantitative and the conversion very high: the product can be recovered pure without any supplementary purification, as the unreacted acid was separated during the workup of the reaction mixture. This methodology is applicable to the synthesis of other *O*-alkylhydroxamates (**6** and **10**, entries 10 and 16) and to the preparation of *O*-silyl hydroxamates too. In this last case it is noteworthy that the method allows an easy preparation of *O*-silyl hydroxamates derived from α-amino acids.[12] The previous syntheses of *O*-silyl hydroxamates started, in fact, from the corresponding acyl chlorides, preventing the preparation of compounds as **9** (Table 1).

Taking into account that CDMT may be an irritating agent for eyes and nose, we checked the possibility of using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[13] (Table 1, method B). Even with this reagent the final products were exclusively the desired Weinreb amides, which can be recovered pure after the simple aqueous workup of the mixture. However, the condensation of the acids with DMTMM requires longer times due to the formation of the activated ester (1.5 h). Moreover, the reactions carried out in the presence of DMTMM proceeded, under the conditions employed (8 h of stirring at room temperature), with conversions lower than those performed with CDMT, with the exception of the reaction with 2-nitrobenzoic acid. In any case, the reactions can be forced to the completion by prolonging the reaction time.

The synthesis of Weinreb amides can be achieved even with the very cheap cyanuric chloride as condensating agent, but the reaction occurs very slowly if conducted following the one-flask procedure, probably owing to the various salts present in the mixture. The reaction can be accelerated by filtering off the precipitate formed on Celite and transferring the THF solution, containing the activated ester, into a flask containing the *N*,*O*-dimethylhydroxylamine hydrochloride THF suspension (Table 1, entry 3).

Significant racemization of the chiral center of the α-amino acids did not occur under the conditions employed, as revealed by the optical rotation values of the products **10** and **12** if compared with those reported in the literature[14,15] (entries 15 and 17).

(1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(2) Lucet, D.; Le Gall, T.; Moskowski, C.; Ploux, O.; Marquet, A. *Tetrahedron: Asymmetry* **1996**, *7*, 985.
(3) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039.
(4) Maugras, I.; Poncet, J.; Jouin, P. *Tetrahedron* **1990**, *46*, 2807. Shreder, K.; Zhang, L.; Goodman, M. *Tetrahedron Lett.* **1998**, *39*, 221.
(5) Braun, M.; Waldmüller, D. *Synthesis* **1989**, 856.
(6) Sibi, M. P.; Stessman, C. C.; Schultz, J. A.; Christensen, J. W.; Lu, J.; Marvin, M. *Synth. Commun.* **1995**, *25*, 1255.
(7) Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* **1986**, *27*, 5467; Dechantsreiter, M. A.; Burkhart, F.; Kessler, H. *Tetrahedron Lett.* **1998**, *39*, 253; Einhorn, J.; Einhorn, C.; Luche, J. L. *Synth. Commun.* **1990**, *20*, 1105.
(8) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091.
(9) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395; Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962; Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275.
(10) Papaioannou, D.; Barlos, K.; Francis, G. W.; Brekke, T.; Aksnes, D. W.; Maartmann-Moe, K. *Acta Chem. Scand.* **1990**, *44*, 189.
(11) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466.
(12) *O*-Silyl hydroxamates are valuable intermediates for the generation of nitrile oxides in solution. See: Muri, D.; Bode, J. W.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 539.
(13) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **1999**, *55*, 13159.
(14) Saari, W. S.; Fisher, T. E. *Synthesis* **1990**, 453.
(15) Sibi, M. P.; Stessman, C. C.; Schultz, J. A. *Synth. Commun.* **1995**, *25*, 1255.

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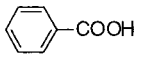
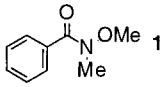
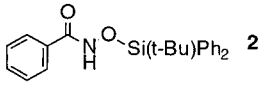
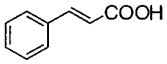
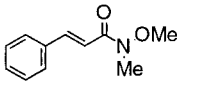
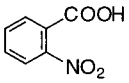
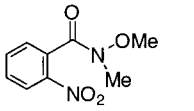
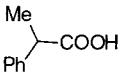
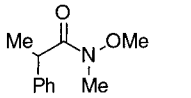
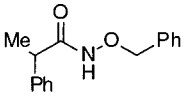
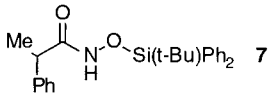
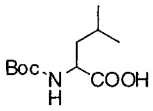
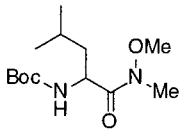
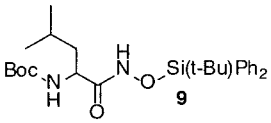
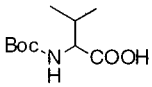
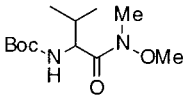
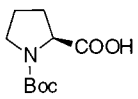
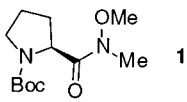
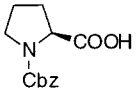
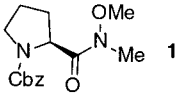
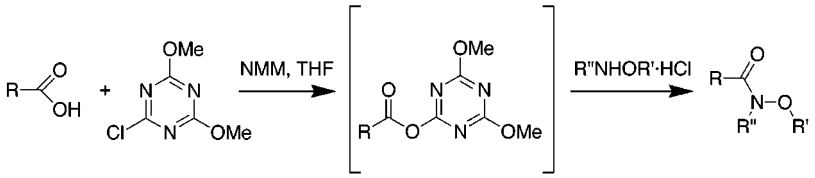
Table 1. Synthesis of Weinreb Amides and Hydroxamates from Carboxylic Acids

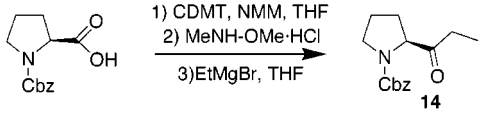
entry	acid	product	method[a]	conversion[b] (%)
1		 **1**	A	85
2	"	"	B	56
3	"	"	C	49
4	"	 **2**	A	83
5		 **3**	A	97
6	"	"	B	80
7		 **4**	B	95
8		 **5**	A	97
9	"	"	B	80
10	"	 **6**	A	89
11	"	 **7**	A	77
12		 **8**	A	97
13	"	"	B	67
14	"	 **9**	A	87
15		 **10**	A	95[c]
16	"		A	97
17		 **12**	A	95[d]
18	"	"	B	53
19		 **13**	A	93
20	"	"	B	76

[a] Method A: with CDMT; method B: with DMTMM; method C: with cyanuric chloride. [b] After 8 h. The yields are quantitative in all the cases described. [c] $[\alpha]^{25}_{D}$ −27.4 (MeOH). [d] $[\alpha]^{25}_{D}$ −36.6 (MeOH).

Scheme 1



Scheme 2



Finally, the THF solution containing the Weinreb amide can be used directly in further reactions without any purification except the simple filtration of the salts formed. For example, a filtered THF solution containing *N*-benzyloxycarbonyl-L-proline-*N*′-methoxy-*N*′-methylamide **13** was added to a THF solution of ethylmagnesium bromide to give the corresponding ethyl ketone **14** in good yield (67% after 0.5 h at room temperature) (Scheme 2).

This method can also be applied to the preparation of hydroxamic acids as demonstrated by the synthesis of the Trichostatine A analogue (**18**, Scheme 3), a powerful cytodifferentiating agent, very promising as a potential cancer chemotherapeutic.[16,18]

N-Boc-aminocaproic acid **15** was converted in good yield (75%) into the corresponding *O*-benzylhydroxamate **16** using DMTMM as the coupling agent (method B). After deprotection of the Boc with TFA, the coupling with *p*-dimethylamino benzoic acid, performed with DMTMM, gave product **17** that was finally transformed into the hydroxamic acid **18** by transfer hydrogenation with Pd/C in refluxing cyclohexene (overall yield 51% from **15**).

In conclusion, we think that the one-flask method described here is one of the most simple and convenient for the preparation of Weinreb amides, hydroxamates and hydroxamic acids even in large scale, as it uses friendly reaction conditions and not expensive reagents. Moreover, this methodology should be an useful addition to parallel synthesis.

Experimental Section

All the solvents and the reagents were used in the commercially available grade of purity. The *N*-protected amino acids were prepared according standard methods and their purity was established before utilization by melting point and optical rotation. Although 2-chloro-4,6-dimethoxy[1,3,5]triazine (CDMT) and 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) are commercially available, we prepared them following a published procedure,[11,17] Cyanuric chloride, *N*,*O*-dimethylhydroxylamine and *O*-benzylhydroxylamine hydrochlorides were purchased from Aldrich. *tert*-Butyldiphenylsilylhydroxylamine was prepared as described.[10]

Optical rotations were measured in a 1 dm tube. The ^{1}H NMR and ^{13}C NMR were obtained at 300/75.4 MHz from $CDCl_3$ solutions.

General Procedure for the Synthesis of Weinreb Amides *N*-Methoxy-*N*-methylbenzamide 1. Method A. To a solution of benzoic acid (0.50 g, 3.7 mmol) in THF (11 mL), at room temperature, were added CDMT (0.74 g, 4.4 mmol) and NMM (1.2 mL, 11.1 mmol). A white precipitate was formed during stirring for 1 h, and then *N*,*O*-dimethylhydroxylamine hydrochloride (0.36 g, 3.7 mmol) was added. The mixture was stirred for additional 8 h and then quenched with 15 mL of H_2O and extracted two times with 7 mL of diethyl ether. The combined organic phases were washed two times with 15 mL of a saturated solution of Na_2CO_3, followed by 15 mL of a solution 1 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 to give, after evaporation of solvent, compound **1** that was isolated pure without other purifications (85%): ^{1}H NMR, δ, 7.66−7.59 (m, 2H), 7.45−7.31 (m, 3H), 3.53 (s, 3H), 3.32 (s, 3H); ^{13}C NMR, δ, 170.2, 134.3, 131.1, 128.2, 123.1, 61.1, 33.9.

Method B. To a solution of benzoic acid (0.50 g, 3.7 mmol) in THF (11 mL), at room temperature, was added DMTMM (0.68 g, 4.8 mmol) and NMM (0.8 mL, 7.4 mmol). A white precipitate was formed during stirring for 1.5 h, and then *N*,*O*-dimethylhydroxylamine hydrochloride (0.36 g, 3.7 mmol) was added. The mixture was stirred for additional 8 h and then worked-up as above to give compound **1** (56%).

Method C. To a solution of benzoic acid (0.5 g, 3.7 mmol) in THF (25 mL), at room temperature, was added the cyanuric chloride (0.73 g, 3.9 mmol) and NMM (1.2 mL, 11.1 mmol). A white precipitate was immediately formed. After stirring for 3 h, the solid formed was filtered off on Celite and the solution containing the activated ester transferred into a flask containing *N*-*O*-dimethylhydroxylamine hydrochloride (0.36 g, 3.7 mmol). The mixture was stirred for additional 8 h and then worked-up as above to give **1** (49%).

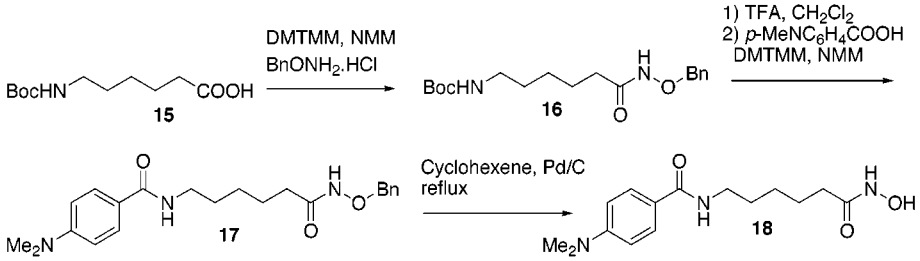
General Procedure for the Synthesis of *O*-Benzyl Hydroxamates. *N*-Benzyloxy-2-phenylpropionamide 6 (Method A). To a solution of 2-phenylpropionic (0.55 g, 3.7 mmol) in THF (11 mL), at room temperature, were added CDMT (0.74 g, 4.4 mmol) and NMM (1.2 mL, 11.1 mmol). A white precipitate was formed during stirring for 1 h, and then *O*-benzylhydroxylamine hydrochloride (0.64 g, 3.7 mmol) was added. The mixture was stirred for additional 8 h and then worked-up as above to give **6** that was isolated pure without other purifications (85%): ^{1}H NMR, δ, 9.14−8.85 (m, 1H), 7.57−7.29 (m, 10H), 4.94 (s, 2H), 3.60 (d, 1H), 1.61 (s, 3H); ^{13}C NMR, δ, 172.0, 140.8, 135.4, 129.6, 128.9, 128.7, 126.7, 126.5, 78.1, 44.0, 18.5. Anal. Calcd for $C_{16}H_{17}NO_2$ (255,31): C, 75,27; H, 6,71; N, 5,49. Found: C, 75.25; H, 6.75, N, 5.52.

General Procedure for the Synthesis of *O*-Silyl Hydroxamates. *O*-*tert*-Butyldiphenylsilylbenzhydroxamate 2. To a solution of benzoic acid (0.50 g, 3.7 mmol) in THF (11 mL), at room temperature, were added CDMT (0.74 g, 4.4 mmol) and NMM (1.2 mL, 11.1 mmol). A white precipitate was formed during stirring for 1 h, and then *tert*-butyldiphenylsilylhydroxylamine (1.08 g, 3.7 mmol) was added. The mixture was stirred for additional 8 h and then quenched with 15 mL of H_2O and extracted two times with 7 mL of ethyl acetate. The combined organic phases were washed two times with 15 mL of a saturated solution of Na_2CO_3, followed by 15 mL of a solution 1 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 to give, after evaporation of solvent, pure **2** (83%) as a white solid: mp 138−139 °C; ^{1}H NMR, δ, 7.84−7.73 (m, 6H), 7.46−7.31 (m, 9H), 1.20 (s, 9H); ^{13}C NMR, δ, 170.2, 134.3, 131.1, 128.2, 123.1, 61.1, 33.9.

***N*-Benzyloxycarbonyl-pyrrolidin-2-yl-propan-1-one 14.** To a solution of *N*-benzyloxycarbonyl-L-proline (0.89 g, 3.7 mmol) in THF (11 mL), at room temperature, were added CDMT (0.74 g, 4.4 mmol) and NMM (1.2 mL, 11.1 mmol). A white precipitate

(16) Jung, M.; Brosh, G.; Kolle, D.; Scherf, H.; Gerhauser, C.; Loidl, P. *J. Med. Chem.* **1999,** *42*, 4669.
(17) Cronin, J. S.; Ginah, F. O.; Murray, A. R.; Copp, J. D. *Synth. Commun.* **1996**, *26*, 3491.
(18) Schmidt, K.; Gust, R.; Jung, M. *Arch. Pharm.* **1999**, *332*, 353.

Scheme 3



was formed during stirring for 1 h, and then *N*,*O*-dimethylhydroxylamine hydrochloride (0.36 g, 3.7 mmol) was added. The mixture was stirred for additional 8 h and then the solid filtered off under argon. The solution was added at room temperature to a THF solution (11 mL) of ethylmagnesium bromide (2.46 mL of 3 N in Et_2O, 2.5 mmol), stirred for additional 0.5 h, and then quenched with aqueous saturated NH_4Cl and extracted two times with 10 mL of diethyl ether. The combined organic phases were washed with 15 mL of a saturated solution of Na_2CO_3, followed by 15 mL of a solution 1 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 to give, after evaporation of solvent, crude *N*-benzyloxycarbonyl-pyrrolidin-2-yl-propan-1-one (85%), that was further purified by flash-chromatography (EtOAc−hexane = 6:4) (67%): $[\alpha]^{20}_D$ −44° (c 0.8, $CHCl_3$); ^{1}H NMR, δ, 7.31 (m, 5H), 5.08 (m, 2H), 4.47−4.26 (m, 1H), 3.62−3.41 (m, 2H), 2.45 (dq, 2H), 2.15 (m, 1H), 1.83 (m, 3H), 1.00 (dt, 3H); ^{13}C NMR, δ, 184.5, 155.3, 137.2, 128.5, 127.6, 67.2, 65.0, 46.9, 32.5, 29.6, 24.1, 7.51. Anal. Calcd for $C_{15}H_{19}NO_3$ (261,32): C, 68.94; H, 7.33; N, 5.36. Found: C, 66.98; H, 7.35, N, 5.39.

***6 N-tert*-Butoxycarbonylamino-hexanoic Acid *N*′-Benzyloxyamide 16.** The product was prepared starting from *N*-*tert*-butoxycarbonyl-hexanoic acid (1.5 g, 6.4 mmol) following general method B. After the hydrolytic workup and evaporation of the solvent, we recovered pure **16** (1.59 g, 77% yield). ^{1}H NMR, δ, 8.37 (s, 1H), 7.30 (s-like 5H), 4.91 (s, 2H), 4.60 (bs, 1H), 3.07 (m, 2H), 1.78 (m, 2H), 1.68−1.25 (m, 6H), 1.42 (s, 9H). ^{13}C NMR, δ, 169.8, 157.7, 139.9, 128.7, 127.3 (2C), 77.7, 70.6, 44.6, 32.9, 30.8, 28.5, 26.7, 24.5. Anal. Calcd for $C_{19}H_{29}N_2O_4$ (336.20): C, 64.36; H, 8.39; N, 8.33 Found C, 64.06, H, 8.40; N, 8.30.

***6-N*-(4-Dimethylaminophenylcabarmoyl)hexanoic Acid *N*′-Benzyloxyamide 17.** Compound **16** (1.53 mg, 4.7 mmol) was dissolved into CH_2Cl_2 (10 mL), and to this solution TFA (6.9 g, 61 mmol) was added followed by triethylsilane (1.37 g, 11.7 mmol). The mixture was stirred for 4 h at room temperatue. The solvent was evaporated and the residue taken up in ether. The white precipitate was filtered and washed several times with ether. This product was added to a solution of NMM (1.28 g, 12.6 mmol) in THF (25 mL) followed by 4-(dimethylamino)-benzoic acid (0.77 g, 4.7 mmol) and DMTMM (1.3 g, 4.7 mmol). The mixture was stirred at room temperature for 8 h. Ethyl acetate (50 mL) was added followed by a solution of Na_2CO_3 and by water. The organic solvent was separated and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The crude product was crystallized from EtOH:H_2O to give pure **17** (86%). Mp 118−119 °C. ^{1}H NMR, δ 8.37 (s, 1H), 7.66 (d, J = 8 Hz, 2H), 7.3 (s-like, 5H), 6.66 (d, J = 8 Hz, 2H), 6.09, bs, 1H), 4.90 (s, 2H), 3.41 (m, 2H), 3.00 (s, 6H), 2.08 (m, 2H), 1.60−1.30 (m, 6H), 1.45 (s, 9H).

***N*-Hydroxy-(4-dimethylaminobenzoylamino)capramide 18.** Product (0.5 g, 1.3 mmol) was dissolved in MeOH (10 mL) and cyclohexene (5 mL), and to the solution was added Pd/C 10% (50 mg). The mixture was refluxed for 6 h, the catalyst was filtered and washed with MeOH, and the solvent was evaporated. The crude was dissolved in the lowest amount of MeOH, and product **18** was separated as a white solid by slow addition of Et_2O (77%). Mp 166−167 (lit.[18] mp 170 °C). The compound showed the same spectoscopical properties described in the literature.[18]

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Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **3**−**5** and **7**−**13** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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