A facile synthesis of *N*-Fmoc protected amino/peptidyl Weinreb amides employing acid chlorides as key intermediates

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Abstract
An efficient, cost effective method for the preparation of *N*-Fmoc α-amino/ peptidyl Weinreb amides from the corresponding acid chlorides has been described. The synthesis of acid chlorides was accelerated by ultrasonication and were coupled with *N,O*-dimethylhydroxylamine hydrochloride to obtain the title compounds. All the prepated compound were isolated as stable solids after workup and have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Keywords: Weinreb amides, *N,O*-dimethylhydroxylamine, *N*-Fmoc α-amino acids/ peptide acids, acid chlorides, ultrasonication

Introduction

Weinreb amides[1] are among the classes of versatile compounds which show a wide applicability.[2] These *N*-methoxy-, *N*-methyl amides have drawn much attention owing to their reactivity with nucleophiles, their selective reduction into aldehydes and also their utility in the preparation of ketones upon reaction with Grignard reagents.[3] The utility of the Weinreb amides has also flourished in peptide chemistry. Much of their application in this field stems from the need for *N*-protected amino aldehydes which are important intermediates for many chemo selective transformations.[4] They are also useful in the synthesis of acetylenes[5] which are starting materials for the popular click reactions.[6] Reduction of Weinreb amides derived from *N*-protected amino acids gives the corresponding aldehydes readily and this would give a better protocol for the synthesis of *N*-Fmoc-α-amino aldehydes which otherwise have to be synthesized either through the oxidation of corresponding alcohols or by careful reduction of esters.[7] Most of the methods for converting carboxylic acids into the corresponding Weinreb amides follow the method of activation of the carboxylic group mainly *via* a mixed anhydride using chloroformates followed by coupling with *N,O*-dimethylhydroxylamine.[8] Several common peptide coupling

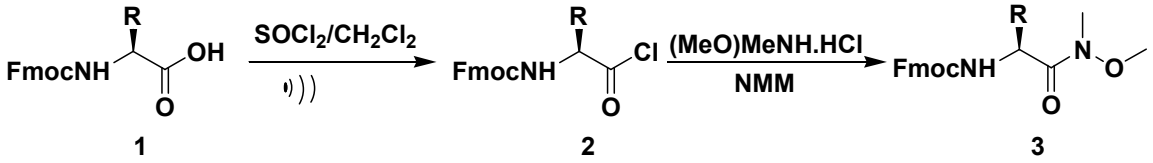
reagents such as BOP[9], DCC[10], CDMT, DMTMM[11], etc., are some of the other alternatives for this transformation. But many of the methods discussed here suffer from some of the disadvantages namely longer reaction time, high reaction temperature, difficult product isolation steps, low yields, expensive reagents, multi step reactions, *etc*.

In one of the recent reports, Katritzky *et al.,* have synthesized Boc protected amino Weinreb amides through the corresponding acyl benzotriazoles.[12] The reaction of *N*-acyl benzotriazole and *N,O*-dimethylhydroxylamine hydrochloride at reflux yielded the corresponding Weinreb amide. Giacomelli *et. al,* synthesized *N*-Boc α-amino Weinreb amides using 2-chloro-4,6-dimethoxy-[1,3,5]triazine.[13] Recently one pot synthesis of *N*-Boc α-amino Weinreb amides through acid fluorides as key intermediates employing [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor) has also been reported.[14] As mentioned before, here also, the expensive nature of the reagents make the method less attractive especially in large scale preparations. Therefore, the development of an efficient and cost effective method for the synthesis of *N*-protected amino acid derived Weinreb amides is desirable. Herein we wish to report an efficient synthesis of *N*-Fmoc α-amino acid/ peptide acid derived Weinreb amides using the corresponding acid chlorides.

Results and Discussion

Acid chlorides are inexpensive, highly reactive intermediates which are easy to prepare and isolate. So also the Fmoc α-amino acid chlorides,[15] are easy to prepare, isolable as stable solids and can be stored for a long time. Carpino *et al*., have reported the synthesis of Fmoc α-amino acid chlorides and demonstrated their utilization in peptide synthesis.[16] The high degree of activation and racemisation free coupling has made them attractive intermediates in peptide synthesis. They have been used as efficient acylating agents in Schotten-Baumann and non Schotten-Baumann conditions as well.[17] A number of applications of Fmoc α-amino acid chlorides in peptide synthesis have been reported by our group. Coupling reaction of Fmoc α-amino acid chlorides with amino acid esters under neutral condition was reported utilizing several non basic reagents such as commercial zinc dust,[18] AgCN,[19] KOBt (Potassium salt of 1-hydroxy-7-benzotriazole),[20] TBDMS-OBt (1-(t-butyldimethylsilyloxy)benzotriazole)[21] in the synthesis of peptides. The racemization free synthesis of bioactive peptides such as [Leu]enkephalin,[22] β-casomorphin[23] under neutral conditions demonstrates another utility of these acid chlorides in peptide chemistry. The required acid chlorides for the present study were synthesized by the reaction of thionyl chloride with Fmoc α-amino acids in an aprotic solvent such as dichloromethane. The reaction was carried out under ultrasonication as reported by us[24] and the products were obtained within 30 min. Use of a sonic bath reduced the reaction time to a greater extent which otherwise would take 4-5 h in reflux conditions and more than 24 h at room temperature. All the *N* -Fmoc α-amino acid chlorides **2** were isolated as white solids after solvent evaporation under reduced pressure followed by precipitation in hexane.

For the preparation of title compounds **3**, initially we carried out reactions taking *N*-Fmoc-alanyl chloride as an example. In a typical reaction, *N,O*-dimethylhydroxylamine (1.1 mmol) in CH_2Cl_2 neutralized with *N*-methylmorpholine (1.5 mmol) (NMM) was added to the previously cooled solution of Fmoc-Ala-Cl (1 mmol) in THF. Additional NMM (1.5 mmol) was added to neutralize the liberated HCl from the coupling reaction of the acid chloride and the amine. The reaction was monitored by TLC and was found to be complete within an hour. After a simple work up, the product **3b** was isolated as pure colourless oil which solidified on standing (**Scheme 1**).

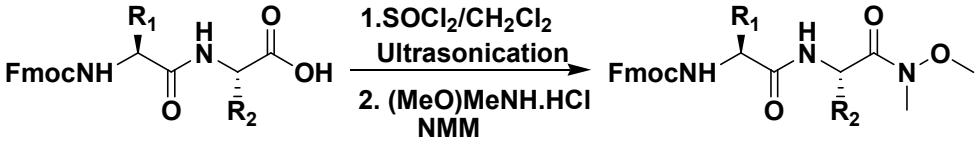


1 2 3

Scheme 1

The same protocol has been then extended to a series of Fmoc protected amino acid chlorides as well (**3a-j**). No side reaction was observed during the course of the reaction. More importantly, no column purification is needed for the isolation of the product. The purity of all the synthesized compounds was more than 98% and were found to be free from racemization as determined by HPLC.

Further, to demonstrate the utility of this protocol, a series of Fmoc protected peptidyl Weinreb amides **5** were also synthesized. Fmoc-peptide acids were converted to the corresponding acid chlorides[25] under ultrasonication as described earlier for their amino acid counterparts and finally coupled with *N,O*-dimethylhydroxylamine to obtain the desired products as white solids after a simple work up. All the synthesized Fmoc peptidyl Weinreb amides have been obtained in good yields and purity (Scheme 2, **5a-e**).



4 5

R1 = -H, $-CH_2C_6H_5$, $-CH_3$, $-CH_2(CH_3)_2$. **R2** = $-CH_2C_6H_5$, $-CH_2CH(CH_3)_2$, $-CH_3$.

Scheme 2

Conclusions

In the present work, we have employed Fmoc α-amino/peptide acid chlorides as precursors for the preparation of Fmoc α-amino/peptidyl Weinreb amides. All the required acid chlorides were synthesized under ultrasonication followed by a coupling reaction with *N,O*-dimethylhydroxylamine hydrochloride to obtain the title products. This two step protocol is a very efficient and cost effective route for the synthesis of Weinreb amides. All the products were isolated after simple work up and were fully characterized by IR, ^{1}H NMR,^{13}C NMR and mass spectroscopy.

Experimental Section

General Procedures. All solvents were freshly distilled before use. Melting points were taken in open capillaries. IR spectra were recorded on a Nicolet model Impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). ^{1}H NMR spectra were recorded on a Bruker AMX 300 MHz spectrometer using Me_4Si as an internal standard and $CDCl_3$ solvent. Mass spectra were recorded on MALDI –TOF (KRATOS).

General procedure for the synthesis of *N*-Fmoc α-amino/peptidyl acid chloride 2
To a solution of Fmoc amino acid (5 mmol) in CH_2Cl_2 (25 mL) was added $SOCl_2$ (15 mmol) and the solution was subjected to ultrasonication for 30 min. The reaction was followed by TLC and after the completion, the reaction mixture was concentrated under *vacuo* and triturated with hexane. The resulting precipitate was filtered and dried under vacuum.

General procedure for the synthesis of *N*-Fmoc α-amino/peptidyl Weinreb amide 3, 5
To a stirred solution of Fmoc amino acid chloride (5 mmol) in THF (30 mL) at 0°C was added *N,O*-dimethylhydroxylamine hydrochloride (6 mmol) neutralized with N-methylmorpholine (NMM) (9 mmol). More of NMM (6 mmol) was added to neutralize the HCl evolved during the reaction. The reaction mixture was stirred at room temperature till completion of reaction. THF was removed and the residue was partitioned between CH_2Cl_2 (20 mL) and a citric acid solution (10%, 15 mL). The organic layer was washed with a sodium carbonate solution (10%, 15mL x 2), water (15 mL) and brine (15 mL). It was dried over anhydrous sodium sulfate and concentrated under vacuum.

***N*$^{\alpha}$-Fmoc-Gly-N(OMe)Me (3a).** White solid (90%); m.p. 108°C; IR (KBr): 1698, 1659 cm^{-1}; ^{1}H NMR δ 3.23 (s, 3H), 3.61 (m, 2H), 3.73(s, 3H), 4.19 (t, 1H), 4.45(d, J= 7.2Hz, 2H), 5.63 (d, J= 12.5Hz, 1H), 7.12-7.75 (m, 8H); ^{13}C NMR δ 34.4, 46.5, 50.2, 59.2, 65.8 120, 125, 137, 140, 147.2, 155, 160, 171; HRMS found for $C_{19}H_{20}N_2NaO_4$: 363.1325.

***N*$^{\alpha}$-Fmoc-Ala-N(OMe)Me (3b).** White solid (86%); m.p. 113°C; IR (KBr):1693, 1662 cm^{-1}; ^{1}H NMR δ 1.36(d, J=11.4Hz, 3H), 3.23 (s, 3H), 3.77 (s, 3H), 4.22 (t, 1H), 4.35(d, J=7.2Hz, 2H), 4.74(m, 1H), 5.59 (d, J= 5.2Hz, 1H), 7.25-7.77 (m, 8H); ^{13}C NMR δ 21.47, 32.0, 47.06, 50.16, 60.61, 69.52, 119.8, 125.1, 127.6, 141.5, 148.9, 152.6, 156.7, 169.5; HRMS found for $C_{20}H_{22}N_2NaO_4$: 377.1472.

***N*$^{\alpha}$-Fmoc-Val-N(OMe)Me (3c).** Off white solid (82%); m.p. 109°C; IR (KBr): 1688, 1650 cm^{-1}; ^{1}H NMR δ 1.25 (d, J=12.5Hz, 6H),1.88 (m, 1H), 3.24 (s, 3H), 3.71(s, 3H), 4.17 (t, 1H), 4.55(d, J=8.2Hz, 2H), 4.81(m, 1H), 5.53 (d, J=6.5Hz, 1H), 7.22-7.85 (m, 8H); ^{13}C NMR δ 18.7, 27.8, 31.6, 39.8, 48.0, 60.7, 69.8, 119.1, 121.2, 130.0, 131.1, 145.2, 151.2, 160, 170.5; HRMS found for $C_{22}H_{26}N_2NaO_4$: 405.1810.

***N*$^{\alpha}$-Fmoc-Leu-N(OMe)Me (3d).** White solid (89%); m.p. 125°C; IR (KBr): 1702, 1638 cm^{-1}; ^{1}H NMR δ 0.94 (m, 6H), 1.33 (m, 2H), 2.1 (m, 1H), 3.35 (s, 3H), 3.70(s, 3H), 4.27 (t, 1H), 4.32(d, J=10.2Hz, 2H), 4.72(m, 1H), 5.62 (d, J=7.2Hz, 1H), 7.12-7.90 (m, 8H); ^{13}C NMR δ 22.8, 23.9, 31.2, 38.3, 39.2, 48.8, 58.1, 63.2, 119.2, 122.2, 131.5, 132.8, 140.5, 145, 156.2, 169.6; HRMS found for $C_{23}H_{28}N_2NaO_4$:419.1951.

***N*$^{\alpha}$-Fmoc-Ile-N(OMe)Me (3e).** White solid (81%); m.p. 118°C; IR (KBr): 1702, 1648 cm^{-1}; ^{1}H NMR δ 0.93 (m, 6H), 1.41 (m, 2H), 1.7 (m, 1H), 3.34 (s, 3H), 3.78(s, 3H), 4.37 (t, 1H), 4.42(d, J=13.5Hz, 2H), 4.70(m, 1H), 5.66 (d, J=11.8Hz, 1H), 7.22-7.85 (m, 8H); ^{13}C NMR δ 13.8, 15.6, 26.8, 31.2, 32.9, 38.3, 39.2, 48.8, 58.1, 119.3, 122.2, 130.5, 130.8, 141.5, 145.2, 156.4, 170.5; HRMS found for $C_{23}H_{28}N_2NaO_4$: 419.1942.

***N*$^{\alpha}$-Fmoc-Asp(OBn)-N(OMe)Me (3f).** Gummy solid (78%); IR (KBr):1700, 1652 cm^{-1}; ^{1}H NMR δ 1.66(d, J=12.5Hz, 2H), 3.24 (s, 3H), 3.80 (s, 3H), 4.19 (t, 1H), 4.35(d, J=6.3Hz, 2H), 4.68(m, 1H), 5.49 (d, J=9.6Hz, 1H), 7.35-7.87 (m, 13H); ^{13}C NMR δ 32, 37.9, 39.8, 45.6, 53.2, 64.2, 69.5, 118.1, 124.3, 127, 128.5, 129.3, 134.2, 141, 142.8, 155.1 156, 171.2, 172.2; HRMS found for $C_{28}H_{28}N_2NaO_6$: 511.1849.

***N*$^{\alpha}$-Fmoc-Glu(OBn)-N(OMe)Me (3g).** Gummy solid (76%); IR (KBr):1708, 1655 cm^{-1}; ^{1}H NMR δ 1.56-1.65(m, 4H), 3.23 (s, 3H), 3.84 (s, 3H), 4.20 (t, 1H), 4.32(d, J=14.0Hz, 2H), 4.70(m, 1H), 5.59 (d, J= 8.6Hz, 1H), 7.25-7.90 (m, 13H); ^{13}C NMR δ 27.2, 31.8, 32, 37.5, 45.2, 52.2, 64.6, 69.5, 119.1, 124.8, 127, 128.5, 130.3, 135.1, 142, 144.8, 152.1 155, 170, 171.3; HRMS found for $C_{29}H_{30}N_2NaO_6$:525.2008.

***N*$^{\alpha}$-Fmoc-Met-N(OMe)Me (3h).** White solid (80%); m.p. 93°C; IR (KBr):1698, 1655 cm^{-1}; ^{1}H NMR δ 1.92(s, 3H), 2.2 (m, 2H), 2.5 (m, 2H), 3.25 (s, 3H), 3.76 (s, 3H), 4.22 (t, 1H), 4.30(d, J=10.2Hz. 2H), 4.52(m, 1H), 5.69 (d, J=8.5Hz, 1H), 7.32-7.90 (m, 8H); ^{13}C NMR δ 16.2, 28.9,32, 33.6, 36.2, 40.1, 44.2, 49.1, 53.5, 118.2, 126.1, 136.8, 143.2, 153.1, 156, 168.2; HRMS found for $C_{22}H_{26}N_2NaO_4S$: 437.1590.

***N*$^{\alpha}$-Fmoc-Phe-N(OMe)Me (3i).** White solid (87%); m.p. 132°C; IR (KBr):1693, 1660 cm^{-1}; ^{1}H NMR δ 2.27-2.45 (m, 2H), 3.22 (s, 3H), 3.77 (s, 3H), 4.22 (t, 1H), 4.35(d, J=9.2Hz, 2H), 4.85(m, 1H), 5.49 (d, J=12.2Hz, 1H), 7.25-7.97 (m, 13H); ^{13}C NMR δ 31.7, 37, 40.1, 44, 51.2, 63, 120.6, 125.5, 126.3, 128.6, 131.5, 132.6, 134, 135, 143, 151.8, 157, 171.2; HRMS found for $C_{26}H_{26}N_2NaO_4$:453.1752.

***N*$^{\alpha}$-Fmoc-(L)Phg-N(OMe)Me (3j).** Off white solid (84%); m.p. 102°C; IR (KBr):1698, 1676 cm^{-1}; ^{1}H NMR 3.32 (s, 3H), 3.87 (s, 3H), 4.19 (t, 1H), 4.35(d, J=10.5Hz, 2H), 4.85(m, 1H), 5.51 (d, J=7.5Hz, 1H), 7.15-7.87 (m, 13H); ^{13}C NMR δ 32, 39.8, 44.1, 47.9, 55, 120.1, 122.2, 126.2, 126.8, 129, 130.5, 133.2, 135, 141, 151.2, 158.5, 170.2; HRMS found for $C_{25}H_{24}N_2NaO_4$: 439.1638.

***N*$^{\alpha}$-Fmoc-Gly-Phe-N(OMe)Me (5a).** White solid (79%); m.p. 110°C; IR (KBr):1700, 1670 cm^{-1}; ^{1}H NMR δ 2.35 (m, 2H), 3.25 (s, 3H), 3.55 (m, 2H), 3.81 (s, 3H), 3.91(m, 1H), 4.74 (m, 1H), 5.69 (d, J=8.6Hz, 1H), 6.18(d, J= 4.2Hz, 1H), 7.22-7.92(m, 13 H); ^{13}C NMR δ 32.1, 37.28, 44.1, 50.3, 53.2, 61.2, 67.2, 119.9, 125.0, 127.7, 128.4, 129.4, 135.8, 141.2, 143.7, 156.7, 168.6, 169.3, 173.7; HRMS found for $C_{28}H_{29}N_3NaO_5$: 510.2010.

***N*$^{\alpha}$-Fmoc-Phe-Leu-N(OMe)Me (5b).** White solid (81%); m.p. 118°C; IR (KBr):1706, 1665 cm^{-1}; ^{1}H NMR δ 0.88 (m, 6H), 1.38 (m, 2H), 2.1(m, 1H), 2.4 (m, 2H), 4.21 (t, 1H), 4.45 (d, J=12.5, 2H), 4.8 (m, 1H), 5.8 (m, 2H), 6.14 (m, 1H), 7.4-7.9 (Ar, 13 H); ^{13}C NMR δ 22.8, 24.1, 32.1, 37.3, 38.2, 44.5, 47.5, 51.3, 52.5, 61.6, 67.2, 120.1, 125.2, 126.7, 128.4, 129.6, 132.5, 144.2, 143.7, 156.7, 168.6, 169.3, 173.7; HRMS found for $C_{32}H_{37}N_3NaO_5$: 566.2628.

***N*$^{\alpha}$-Fmoc-Ala-Phe-N(OMe)Me (5c).** White solid (83%); m.p. 123°C; IR (KBr):1698, 1665 cm^{-1}; ^{1}H NMR δ 1.33 (d, J=11.8Hz, 3H), 2.25 (m, 2H), 3.25 (s, 3H), 3.81 (s, 3H), 3.91(m, 1H), 4.6 (m, 1H), 5.7 (d, J= 13.9Hz, 1H), 6.21(d, J= 8.2Hz, 1H), 7.25-7.95(m, 13 H); ^{13}C NMR δ 21.5, 32.5, 37.1, 38.9, 45.4, 48.5, 50.2, 54.2, 62.2, 67.2, 119.9, 125.0, 127.7, 128.6, 130.1, 136.9, 141.8, 142.7, 156.9, 167.8, 169.1, 171.7; HRMS found for $C_{29}H_{31}N_3NaO_5$: 524.2166.

***N*$^{\alpha}$-Fmoc-Val-Ala-N(OMe)Me (5d).** White solid (87%); m.p. 133°C; IR (KBr):1695, 1671 cm^{-1}; ^{1}H NMR δ 1.21 (d, J=9.3Hz, 6H), 1.32 (d, J=8.2Hz, 3H), 3.35 (s, 3H), 3.81 (s, 3H), 4.11 (t, 1H), 4.41 (d, J=13.2Hz, 2H), 4.82 (m, 2H), 5.61 (m, 1H), 6.21 (m, 1H), 7.1-7.85 (m, 8H); ^{13}C NMR δ 17.7, 21.0, 26.8, 32.6, 39.8, 45.2, 48.5, 61.7, 69.8, 119.1, 121.2, 130.0, 131.1, 145.2, 151.2, 156.2, 161, 171.4; HRMS found for $C_{25}H_{31}N_3NaO_5$: 476.2167.

***N*$^{\alpha}$-Fmoc-Ala-Leu-N(OMe)Me (5e).** White solid (80%); m.p. 140°C; IR (KBr): 1712, 1641 cm^{-1}; ^{1}H NMR δ 0.94 (m, 6H), 1.31 (m, 2H), 1.37 (d, J=14.8Hz, 3H), 2.32 (m, 1H), 3.45 (s, 3H), 3.72(s, 3H), 4.27 (t, 1H), 4.5(d, J=8.2Hz, 2H), 4.82(m, 2H), 5.61 (d, J=6.6Hz, 1H), 6.2 (m, 1H), 7.2-7.8 (m, 8H); ^{13}C NMR δ 20.91, 22.7, 24.1, 32.2, 38.5, 40.1, 48.0, 49.2, 58.1, 64.6, 119.2, 122.3, 131.1, 131.5, 140.1, 144, 155.2, 157.1 169.6; HRMS found for $C_{26}H_{33}N_3NaO_5$: 490.2320.

Acknowledgements

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