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A FACILE ONE-POT SYNTHESIS OF WEINREB AMIDES FROM CARBOXYLIC ACIDS WITH $POCL_3$

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ABSTRACT

Conversion of carboxylic acids to Weinreb amides in one pot by using N,O-dimethyl hydroxylamine hydrochloride and phosphorus (V) oxy-chloride ($POCl_3$) in presence of Hunig's base in dichloromethane at room temperature in excellent yields. This method demonstrated for sterically hindered carboxylic acids and also various functional groups which are tolerated on the carboxylic acids.

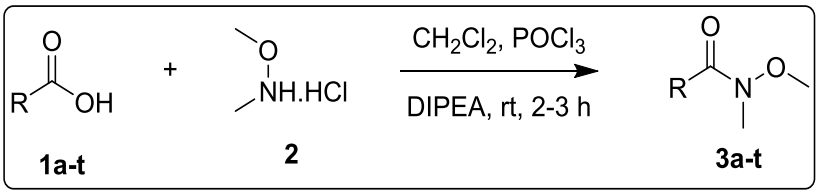
KEYWORDS: Weinreb amides, Phosphorous oxychloride, Hunig's base.

INTRODUCTION

Weinreb amides were synthesised in 1981 by Nahm and Weinreb co-workers[1,2]. Since then the *N*-methoxy-*N*-methylamides (Weinreb amides) were a highly versatile key intermediates for the preparation of aldehydes and ketones,[3,4] and also used in the synthesis of natural products and biologically active substances.[5-7] Several reagents were accessible for conversion of carboxylic acids to Weinreb amides such as 1,1′-carbonyldiimidazole,[8] 1,3-dicyclohexylcarbodiimide/1-hydroxybenzotriazole,[9] oxalyl chloride,[10] benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluoro phosphate,[11] triphenylphosphine/carbon tetrabromide,[12] *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,[13] 2-pyridyl esters[14] and 2-chloro-4,6-dimethoxy-[1,3,5] triazine[15] and also were synthesized from *in situ* mixed phosphonic anhydrides, acid anhydrides, which was generated from the treatment of carboxylic acids with pivaloylchloride,[16] alkyl chloroformates,[17] propylphosphonic acid anhydride[18] or diethyl phosphorocyanidate[19] respectively, by subsequent addition of *N*,*O*-dimethyl hydroxylamine hydrochloride in the presence of base.

However, some of these methods have drawbacks such as longer reaction time, commercially unavailable reagent or toxic, expensive reagents, high temperature, low yields, multi-step reactions and tedious work up procedures. To overcome these disadvantages, here we disclose a very convenient and efficient method for one pot synthesis of Weinreb amides from carboxylic acids by using $POCl_3$ as an acid activator as shown in Scheme 1.

Scheme 1.



Scheme 1: Synthesis of Weinreb amides from carboxylic acids with N,O-dimethyl hydroxylamine hydrochloride and phosphorus (V) oxychloride.

Here we have synthesized a series of Weinreb amides by treating the substituted carboxylic acids (**1a-t**) with *N,O*-dimethyl hydroxylamine hydrochloride (**2**) in presence of *N,N*-diisopropyl-*N*-ethyl amine (DIPEA) and $POCl_3$ in dichloromethane at room temperature for 2-3 hours to afford pure target Weinreb amides (**3a-t**).

MATERIALS AND METHODS

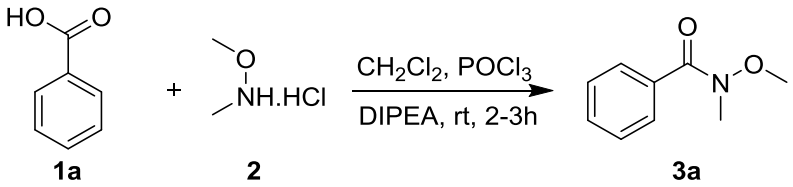
All the chemicals and reagents used for the synthesis, were obtained from commercial sources and were used without any further purification. Reactions were monitored by thin layer chromatography (TLC), performed on silica gel glass plates containing Merck TLC Silica Gel 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}H NMR spectra were recorded in Agilent-400 MHz instrument. ^{13}C NMR spectra were recorded in Agilent-100 MHz. Chemical shifts (δ) are reported in ppm downfield from TMS internal standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI$^+$ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus (Buchi-M-565), and are uncorrected. The infra-red spectra were recorded as potassium bromide disk using Schimadzu-FT-IR spectrophotometer.

RESULTS AND DISCUSSION

We have optimized reaction conditions by using benzoic acid with $POCl_3$ (see Table 1), at room temperature. We have examined the effects of solvents on the reaction. Toluene and

DCM was used as the solvent. Observed progress of the reaction in toluene but the yield is lower than the DCM (Table 1, entry 1 and 2). Hence, we have chosen DCM as optimal solvent for this conversion and varied the mole ratio of phosphorus (V) oxy-chloride, Weinreb amine and DIPEA, had a great effect on the yields of products. However, it was found that the reaction provided the best result with 87% yield (Table 1, entry 6). It was observed that there is no effect on the reaction yield by increasing the equivalents of DIPEA (Table 1, entry 7). We have also performed a reaction by using free base of N,O-dimethyl hydroxylamine in the absence of DIPEA and observed no reaction (Table 1, entry 8). Thus, DIPEA was an effective base for trapping of the HCl, which is generating during the course of reaction.

Table 1: Optimization of the Reaction Conditions.



1a 2 3a

Entry	1a (mmol)	$POCl_3$ (mmol)	2 (mmol)	DIPEA (mmol)	Solvent[a]	Time (h)	Temp (°C)	Yield[b] (%)
1	4	4	4	8	toluene	16	25	45
2	4	4	4	8	CH_2Cl_2	10	25	60
3	4	4.4	4	8	CH_2Cl_2	8	25	65
4	4	4.4	4	10	CH_2Cl_2	6	25	69
5	4	4.4	4.8	10	CH_2Cl_2	4	25	77
6	4	4.4	4.8	12	CH_2Cl_2	2	25	87
7	4	4.4	4.8	16	CH_2Cl_2	2	25	87
8	4	4.4	12[c]	0	CH_2Cl_2	16	25	-

[a] All solvents were purified and dried by standard procedures.

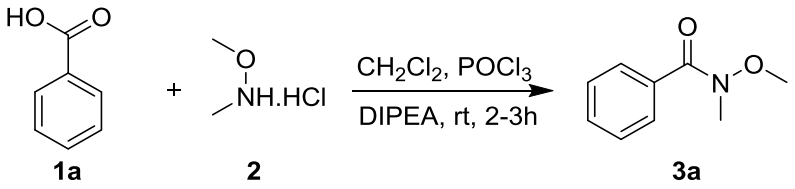
[b] Isolated yield after column chromatography.

[c] NHMe(OMe) free amine was used instead of HCl salt.

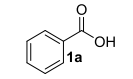
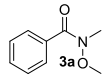
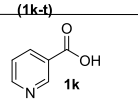
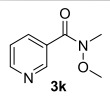
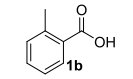
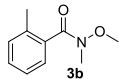
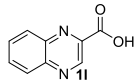
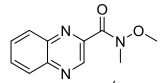
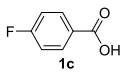
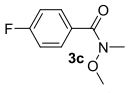
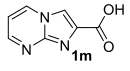
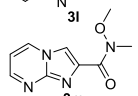
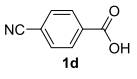
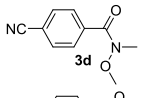
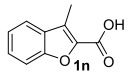
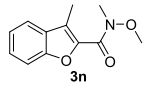
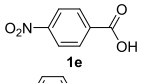
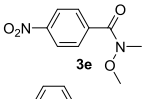
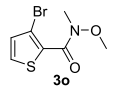
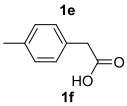
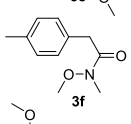
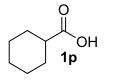
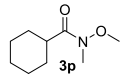
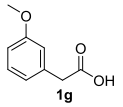
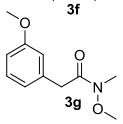
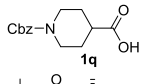
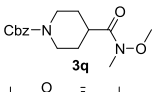
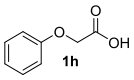
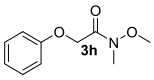
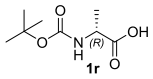
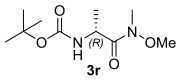
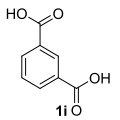
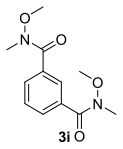
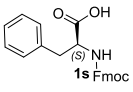
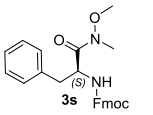
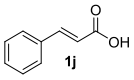
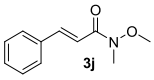
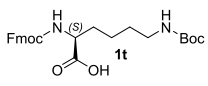
To investigate the efficiency of this method, we have also tried different benzoic acids with electron-donating and electron withdrawing groups on the aryl ring (Table 2, entries 1-5). The electronic effects of the substituent's on the benzoic acids does not affect the reaction yield. A variety of Weinreb amides were synthesized from benzyl (Table 2, entries 6-7), hetero aromatic carboxylic acids (Table 2, entries 11-15) and aliphatic carboxylic acids (Table 2, entry 18). This methodology also applicable on a variety of carboxylic acids with

sensitive functional groups of *N*-protected amino acids (Table 2, entries 17-20) and observed high yields. In all cases, the formation of Weinreb amide was monitored by disappearance of the starting acid by TLC analysis. The reaction was completed in 2-3 hours at room temperature. The crude products were purified by short path silica gel column chromatography. The results are resumed in Table 2.

Table 2: Preparation of Weinreb Amides.



1a 2 3a

Entry	Acid (1a-1j)	Product (3a-j)	Time (h)	Yield (%)[a]	Entry	Acid (1k-t)	Product (3k-t)	Time (h)	Yield (%)[a]
1			2	87	11			3	87
2			2	82	12			2	88
3			2	88	13			3	85
4			2	90	14			3	86
5			2	90	15			2	90
6			2	92	16			2	92
7			2	89	17			2	90
8			2	88	18			2	92
9			3	85	19			2	91
10			2	85	20			3	87

[a] Isolated yield after column chromatography.

EXPERIMENTAL SECTION

General Procedure

***N*-Methoxy-*N*-methylbenzamide (3a):** A solution of N,O-dimethyl hydroxylamine hydrochloride (0.96 g, 9.8 mmol) and benzoic acid (1 g, 8.2 mmol) was stirred in dichloro

methane (15 mL) at 0 °C for 5 min. Then DIPEA (3.18 g, 24.6 mmol) was added drop wise to the mixture at 0°C and followed by added $POCl_3$ (1.38 g, 9.01 mmol) drop wise at 0 °C. The resulted reaction mixture was allowed to r.t. and stirred for 2 h. On completion of the reaction (TLC monitoring), the mixture was cooled to 0 °C and was then quenched with sat. $NaHCO_3$ solution (80 mL), extracted with DCM (2 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The product was purified by column chromatography (silica gel, petroleum ether–EtOAc, 3:2) to afford pure **3a** as colorless oil; Yield: 1.18 g (87%).

The corresponding acids were converted in to weinreb amides using above general procedure (**3a-t**). The final structures of compounds were confirmed by ^{1}H NMR, ^{13}C NMR, M.p, FT-IR, MS, and HRMS.

Spectral data for products (3a-3t)

***N*-Methoxy-*N*-methylbenzamide (3a)**[20]

Colorless oil; yield: 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 - 7.64 (m, 2H), 7.50 - 7.36 (m, 3H), 3.56 (s, 3H), 3.36 (s, 3H).^{13}C NMR (75 MHz, CDCl3) δ= 169.7, 133.9, 130.3, 127.9, 127.8, 60.8, 33.6. FT-IR (KBr): γmax3059, 2970, 2936, 1644, 1576, 1447, 1416, 1380, 1214 cm–¹.MS (ESI): (*m/z*) 166 $[M+H]^+$, HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_{12}NO_2$: 166.0790; found: 166.0860[M+H]+.

N-methoxy-N,2-dimethylbenzamide (3b)[20]

Colorless oil; yield: 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 - 7.12 (m, 4H), 3.50 (br s, 3H), 3.27 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 172.6, 134.9, 134.4, 129.8, 128.8, 125.8, 125.1, 60.7, 32.8, 18.7. FT-IR (KBr): γmax3063, 2970, 2935, 2819, 1652, 1604, 1455, 1416, 1379, 1221, 1198, 1062, 986, 888, 772 cm–¹. MS (ESI): (m/z) 180 $[M+H]^+$,HRMS (ESI): m/z $[M + H]^+$calcd for $C_{10}H_{14}NO_2$: 180.0946; found: 180.1084.

4-fluoro-N-methoxy-N-methylbenzamide (3c)[21]

Colorless oil; yield: 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.79 - 7.70 (m, 2H), 7.14 - 7.04 (m, 2H), 3.54 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.3, 165.3, 162.0, 130.5, 130.4, 129.7, 114.8, 114.5, 60.7, 33.2. FT-IR (KBr): γmax3070, 2971, 2937, 1644, 1605, 1507, 1419, 1379, 1292, 1225, 1158, 1064, 979, 848, 752 cm–¹. MS (ESI): (m/z) 184 [M+H]+,HRMS (ESI): m/z [M + H] +calcd for $C_9H_{11}FNO_2$: 184.0696; found: 184.0764.

4-cyano-N-methoxy-N-methylbenzamide (3d)[20]

White solid; yield: 90%; mp 78-79°C.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 - 7.75 (m, 2H), 7.74 - 7.68 (m, 2H), 3.53 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 167.8, 138.2, 131.8, 128.8, 118.0, 114.0, 61.2, 33.1. FT-IR (KBr): γmax2974, 2938, 2819, 2230, 1651, 1560, 1506, 1421, 1461, 1383, 1215, 980cm–¹. MS (ESI): (m/z) 191 [M+H]+,HRMS (ESI): m/z [M + H]+ calcd for $C_{10}H_{11}N_2O_2$: 191.0776; found: 191.0809.

***N*-methoxy-*N*-methyl-4-nitrobenzamide (3e)[20]**

White solid; yield: 90%; mp 72-73°C.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 - 8.22 (m, 2H), 7.91 - 7.78 (m, 2H), 3.57 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 167.3, 148.4, 139.9, 128.8, 128.6, 122.8, 60.1, 32.8. FT-IR (KBr): γmax 3257, 3225, 3115, 2986, 2941, 1637, 1601, 1526, 1460. 1425, 1355, 1212, 976 cm–¹. MS (ESI): (m/z)211 [M+H]+,HRMS (ESI): m/z [M + H]+ calcd for $C_9H_{11}N_2O_4$: 211.0674; found: 211.0704.

***N*-methoxy-*N*-methyl-2-(p-tolyl) acetamide (3f)[22]**

Colorless oil; yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 - 7.01 (m, 4H), 3.73 (s, 3H), 3.60 (s, 3H), 3.18 (s, 2H), 2.38 - 2.17 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ= 176.1, 136.7, 136.3, 131.7, 130.6, 129.3, 128.1, 61.5, 40.7, 38.9, 32.3, 21.0. FT-IR (KBr): γmax3087, 3004, 2970, 2933, 1728, 1660, 1515, 1438, 1438, 1383, 1172, 1006cm–¹. MS (ESI): (m/z) 194 [M+H]+,HRMS (ESI): m/z [M + H] +calcd for $C_{11}H_{16}NO_2$: 194.1103; found: 194.1171.

***N*-methoxy-2-(3-methoxyphenyl)-*N*-methylacetamide (3g)[23]**

Light yellow oil; yield: 89%.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 - 7.19 (m, 1H), 6.91 - 6.84 (m, 2H), 6.82 - 6.76 (m, 1H), 3.79 (s, 3H), 3.75 (s, 2H), 3.61 (s, 3H), 3.19 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ= 172.1, 159.5, 136.2, 129.2, 121.5, 114.7, 112.2, 61.1, 60.2, 55.0, 39.2, 32.1, 20.8. FT-IR (KBr): γmax3496, 2939, 2836, 1660, 1599, 1490, 1382, 1259, 1150, 1048, 937 cm–¹. MS (ESI): (m/z)210 [M+H]+,HRMS (ESI): m/z [M + H] +calcd for $C_{11}H_{16}NO_3$: 210.1052; found: 210.1115.

***N*-methoxy-*N*-methyl-2-phenoxyacetamide (3h)[24]**

Light yellow oil; yield: 88%.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 - 7.21 (m, 2H), 7.02 - 6.86 (m, 3H), 4.81 (s, 2H), 3.76 (s, 3H), 3.24 (s, 3H). FT-IR (KBr): γmax3504, 2939, 1683, 1955, 1588, 1495, 1440, 1392, 1224, 1176, 1063, 988 cm–¹. ^{13}C NMR (75 MHz, $CDCl_3$) δ= 169.1, 157.9, 129.2, 121.2, 114.3, 65.2, 61.3, 32.1.MS (ESI): (m/z)196 [M+H]+,HRMS (ESI): m/z [M + H] +calcd for $C_{10}H_{14}NO_3$: 196.0895; found: 196.0958.

N^1,N^3-dimethoxy-N^1,N^3-dimethylisophthalamide (3i)[20]

White solid; yield: 85%; mp 42-43°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 7.78 (dd, J = 1.7, 7.6 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 3.55 (s, 6H), 3.37 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.6, 133.5, 130.0, 127.7, 127.6, 60.8, 33.3. FT-IR (KBr): γmax3449, 2934, 1643, 1416, 1379, 1260, 1275, 1175, 978 cm–¹. MS (ESI): (m/z)253 [M+H]+,HRMS (ESI): m/z [M + H]+ calcd for $C_{12}H_{17}N_2O_4$: 253.1110; found: 253.1176.

***N*-methoxy-*N*-methylcinnamamide (3j)[25]**

Light yellow oil; yield: 85%.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, J = 15.7 Hz, 1H), 7.57 (dd, J = 1.5, 7.3 Hz, 2H), 7.42 - 7.33 (m, 3H), 7.04 (d, J = 15.7 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 166.7, 143.2, 134.9, 129.6, 128.5, 127.7, 115.5, 61.6, 32.2. FT-IR (KBr): γmax3489, 3060, 3027, 2967, 2937, 2819, 1706, 1655, 1618, 1578, 1497, 1450, 1415, 1381, 1261, 1178, 1098, 997, 762 cm–¹. MS (ESI): (m/z)192 [M+H]+,HRMS (ESI): m/z [M + H]+ calcd for $C_{11}H_{14}NO_2$: 192.0946; found: 192.1010.

***N*-methoxy-*N*-methyl nicotinamide (3k)[26]**

Light yellow oil; yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.96 (d, J = 1.5 Hz, 1H), 8.69 (dd, J = 1.5, 4.9 Hz, 1H), 8.03 (td, J = 1.9, 7.9 Hz, 1H), 7.36 (dd, J = 4.9, 7.8 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 166.9, 150.8, 148.7, 135.6, 129.4, 122.6, 60.8, 32.7. FT-IR (KBr): γmax 3483, 2971, 2936, 1644, 1590, 1414, 1384, 1260, 1223, 1071, 978, 821 cm–¹. MS (ESI): (m/z) 167 [M+H]+, HRMS (ESI): m/z [M + H] +calcd for $C_8H_{11}N_2O_2$: 167.0742; found: 167.0815.

***N*-methoxy-*N*-methyl quinoxaline-2-carboxamide (3l)[new]**

Light yellow oil; yield: 88%.^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.12 (br s, 1H), 8.23 - 8.08 (m, 2H), 7.94 - 7.76 (m, 2H), 3.81 (br s, 3H), 3.48 (br s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 144.0, 142.6, 140.8, 131.0, 130.5, 129.7, 129.2, 61.8, 32.7. FT-IR (KBr): γmax 3459, 2981, 2933, 1654, 1478, 1386, 1262, 1066, 968, 750 cm–¹. MS (ESI): (m/z)218 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_{11}H_{11}N_3O_2$: 218.0851; found: 218.0920.

***N*-methoxy-*N*-methyl imidazo[1,2-a]pyrimidine-2-carboxamide (3m)[new]**

Yellow solid; yield: 85%; mp 91-93°C.^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.79 (br d, J = 6.2 Hz, 1H), 8.74 (br d, J = 1.8 Hz, 1H), 8.43 (s, 1H), 7.29 (dd, J = 4.2, 6.8 Hz, 1H), 3.79 (s, 3H), 3.29 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ= 159.7, 152.5, 149.5, 141.2, 136.5, 114.6, 110.4, 61.0, 32.3.FT-IR (KBr): γmax3196, 3154, 3133, 2986, 2925, 1783, 1599, 1620, 1516,

1268, 1290, 1178, 1029, 968, 896, 866, 814, 781, 734 cm–¹.MS (ESI): (m/z)207 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_9H_{11}N_4O_2$: 207.0804; found: 207.0871.

_N_-methoxy-_N_,3-dimethylbenzofuran-2-carboxamide (3n)[27]

Light yellow solid; yield: 86%; mp 71-72°C.^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.58 (d, J = 8.0 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.41 - 7.34 (m, 1H), 7.30 - 7.22 (m, 1H), 3.84 (s, 3H), 3.36 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 161.8, 153.5, 142.6, 128.7, 126.5, 123.1, 122.6, 120.3, 111.4, 61.6, 33.9, 8.9. FT-IR (KBr): γmax3061, 2976, 2934, 2818, 1646, 1596, 1448, 1377, 1337, 1250, 1206, 1125, 989, 874, 791, 745 cm–¹. MS (ESI): (m/z)220 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_{12}H_{14}NO_3$: 220.0895; found: 220.0964.

3-bromo-_N_-methoxy-_N_-methylthiophene-2-carboxamide (3o)[28]

Yellow oil; yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 4.9 Hz, 1H), 7.06 (d, J = 5.4 Hz, 1H), 3.70 (s, 3H), 3.36 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ= 161.4, 131.2, 129.3, 126.8, 115.2, 61.4, 33.3. FT-IR (KBr): γmax 3104, 2974, 2935, 2817, 1644, 1634, 1495, 1372, 1275, 1201, 1185, 1050, 979, 871, 804 cm–¹. MS (ESI): (m/z)249.9 [M+H]+,HRMS (ESI): m/z [M + H]+ calcd for $C_7H_9BrNO_2S$: 249.9459; found: 249.9519.

_N_-methoxy-_N_-methylcyclohexanecarboxamide (3p)[20]

Colorless oil; yield: 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.70 (s, 3H), 3.17 (s, 3H), 2.68 (br t, J = 11.3 Hz, 1H), 1.86 - 1.64 (m, 5H), 1.58 - 1.40 (m, 2H), 1.38 - 1.17 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 177.1, 61.2, 39.7, 32.0, 29.4, 28.7, 25.5. FT-IR (KBr): γmax2855, 2932, 1660, 1451, 1275, 994, 764, 749 cm–¹. MS (ESI): (m/z)172 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_9H_{18}NO_2$: 172.1259; found: 172.1327.

Benzyl 4-(methoxy (methyl) carbamoyl) piperidine-1-carboxylate (3q)[29]

Light yellow oil; yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 - 7.29 (m, 5H), 5.13 (s, 2H), 4.28 - 4.17 (m, 2H), 3.71 (s, 3H), 3.18 (s, 3H), 2.93 - 2.79 (m, 3H), 1.79 - 1.65 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 175.2, 155.0, 136.6, 128.3, 127.7, 127.6, 66.9, 61.4, 43.0, 43.2, 37.7, 32.1, 29.5, 27.7. FT-IR (KBr): γmax2937, 2890, 1698, 1660, 1429, 1354, 1275, 1225, 1131, 991, 750, 699cm–¹. MS (ESI): (m/z)307 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_{16}H_{23}N_2O_4$: 307.1580; found: 307.1635.

***Tert*-butyl (R)-(1-(methoxy(methyl) amino)-1-oxopropan-2-yl) carbamate (3r)[30]**

White solid; yield:92%; mp 65-68°C.^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.30 (br d, J = 6.4 Hz, 1H), 4.68 (br s, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.44 (s, 9H), 1.31 (d, J = 6.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ= 173.6, 155.1, 61.5, 54.8, 46.5, 42.9, 38.5, 32.1, 28.5, 28.3, 28.1, 18.6, 12.4. FT-IR (KBr): γmax 3297, 3049, 3006, 2980, 2937, 2914, 2821, 1708, 1661, 1542, 1454, 1389, 1366, 1297, 1253, 1183, 1121, 1066, 980, 865, 756 cm–¹. MS (ESI): (m/z) 234 [M+H]+.

(9H-fluoren-9-yl)methyl (S)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3s)[31]

White solid; yield: 91%; mp 132-133°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, J = 7.3 Hz, 2H), 7.55 (br t, J = 8.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.32 - 7.21 (m, 5H), 7.17 (br d, J = 7.3 Hz, 2H), 5.66 (br d, J = 8.8 Hz, 1H), 5.03 (br d, J = 6.8 Hz, 1H), 4.36 (br dd, J = 7.3, 10.3 Hz, 1H), 4.30 - 4.21 (m, 1H), 4.21 - 4.13 (m, 1H), 3.66 (s, 3H), 3.44 (s, 1H), 3.22 (s, 3H), 3.24 - 3.07 (m, 1H), 2.94 (br dd, J = 7.3, 13.7 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ= 171.8, 155.7, 143.7, 141.1, 136.2, 129.3, 128.3, 127.5, 126.9, 126.8, 125.1, 125.0, 119.8, 66.8, 61.4, 51.9, 50.6, 47.0, 38.5, 31.9. FT-IR (KBr): γmax3299, 3062, 3028, 2939, 1719, 1656, 1449, 1390, 1248, 1043, 986, 740 cm–¹. MS (ESI): (m/z)431 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_{26}H_{27}N_2O_4$: 431.1893; found: 431.1958.

(9H-fluoren-9-yl) methyl tert-butyl (6-(methoxy (methyl) amino)-6-oxohexane-1,5-diyl)(S)-dicarbamate (3t)[31]

White solid; yield: 87%; mp 123-125°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (br d, J = 7.3 Hz, 2H), 7.68 - 7.56 (m, 2H), 7.46 - 7.24 (m, 5H), 5.58 (br d, J = 8.8 Hz, 1H), 4.81 - 4.51 (m, 2H), 4.37 (br d, J = 6.9 Hz, 2H), 4.28 - 4.17 (m, 1H), 3.77 (s, 3H), 3.22 (s, 3H), 3.11 (br d, J = 5.1 Hz, 2H), 1.85 - 1.70 (m, 2H), 1.67 - 1.32 (m, 14H), 0.99 - 0.78 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ= 172.6, 156.1, 155.9, 143.9, 143.7, 141.2, 128.0, 127.6, 127.0, 125.1, 119.9, 79.0, 66.9, 61.6, 50.6, 47.1, 40.2, 32.4, 32.0, 29.6, 29.5, 28.3, 22.4. FT-IR (KBr): γmax3329, 2930, 2861, 1712, 1519, 1451, 1366, 1250, 1172, 990, 759, 743cm–¹. MS (ESI): (m/z)512 [M+H]+,HRMS (ESI): m/z [M + H] + calcd for $C_{28}H_{38}N_3O_6$: 512.2682; found: 512.2749.

CONCLUSION

In summary, we have developed a practical and scalable one pot procedure for the conversion of various carboxylic acids to their corresponding Weinreb amides using $POCl_3$ as an acid activator. The current procedure described here offers high yields of products, the reaction

was also applicable to the preparation of α-amino Weinreb amides and proceeded without deprotection of the N-Boc and N-Fmoc protecting groups, and high resistance to racemization, short reaction time, and operational simplicity.

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