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Conversion of Alanine and Phenylalanine into Weinreb Amides by Using Different Protecting Groups

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Efficient conversions of amino acids into Weinreb amides were achieved by treatment of amino acids with N, O-dimethylhydroxylamine hydrochloride in basic media. The amino group (-NH_2) of amino acids were protected with *p*-toluene sulphonyl chloride (-OTs) and diphenyl phosphinic chloride (-dpp) to get high yield of the product. The products were purified by flash chromatography and characterized by spectroscopic techniques.

Keywords: Weinreb amides, *p*-Toluene sulphonyl chloride, Diphenyl phosphinic chloride.

INTRODUCTION

Weinreb and Nahm[1] designed a method in 1981 to synthesize N-methoxy-N-methylamides (Weinreb amides) and ketones. This functional group has been widely used as versatile synthetic intermediates in organic synthesis[2]. Recently, increasing attention has been paid to N-methoxy-N-methylamides (Weinreb amides) owing to their versatile reactivity with nucleophiles and selective reduction to aldehydes. Weinreb amides derived from amino acids have found extensive use in the preparation of α-amino aldehydes[3] and α-amino ketones[4]. Most direct conversions of carboxylic acids into the corresponding Weinreb amides have utilized peptide-coupling reagents such as benzotriazol-1-yl-N-oxy-tris- (dimethylamino) phosphonium hexafluorophosphate (BOP)[5] N,N'-dicyclohexylcarbodiimide (DCC)[6] or propylphosphonic anhydride/N-ethyl morpholine[7].

In synthetic organic chemistry appropriate protecting groups are required to prevent the formation of undesired bonds and side reactions[8,9]. However tosyl group (-OTs) is extensively used in -NH_2 protection and -OH protection in amino acids and amino alcohols. Tosylamine is the intermediate, when -NH_2 group is protected with tosyl group. This intermediate leads to form weinreb amides and other novel annulated products. At the end of the reaction -Ts group is removed in acidic media. Since diphenyl phosphinic chloride (-dpp) protected weinreb amides are not reported in the literature. In this research along with tosyl group, -dpp group is used in protection of -NH_2 group which leads to form weinreb amides. At the end of the reaction -dpp group is removed in very weak acidic media.

EXPERIMENTAL

Carboxylic acids including alanine, phenyl alanine, *p*-toluene sulphonyl chloride, diphenyl phosphinic chloride, N, N-dicyclohexyl carbodiimide and other solvents of analytical grade were purchased from sigma Aldrich.

Synthesis of tosyl alanine (Fig. 1) (3): To the suspension of D-alanine (1 g, 11.2 mmol) in 25 mL water at room temperature, NaOH (1.34 g, 33.6 mmol) and *p*-toluene sulfonyl chloride (2.56 g, 13.4 mmol) were added[10]. The mixture was stirred at 60 °C for 6 h. The combined basic layers were cooled to 0 °C and acidified (pH = 1) by the addition of conc. HCl. The precipitates were collected by filtration, washed with cold water and air dried to give tosyl alanine as a white solid (0.90 g, 33 %).

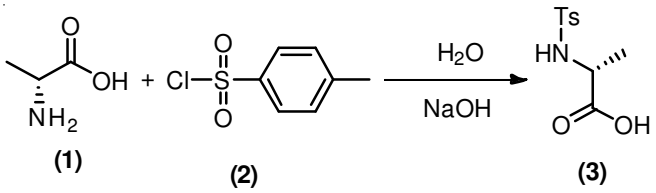


Fig. 1. Synthesis of tosylalanine

Synthesis of weinreb amide of tosyl alanine (Fig. 2) (5): A solution of D or L-Tosyl alanine (1 g, 4.11 mmol), N-methyl morpholine (0.45 g, 4.53 mmol), N,O-dimethylhydroxylamine. HCl (0.44 g, 4.53 mmol) in anhydrous CH_2Cl_2 (16.6 mL) is cooled to 0 °C under argon and treated with N,N-dicyclohexyl carbodiimide (0.93 g, 4.53 mmol) portion wise over 10 min[11]. Stirring was done at 0 °C for 3 h followed by a

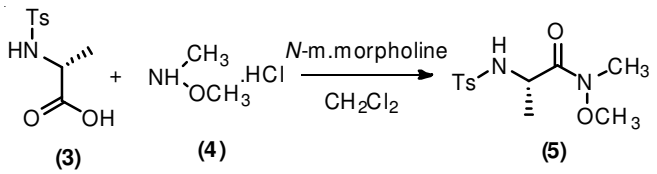


Fig. 2. Synthesis of weinreb amide

further 15 h at room temperature, then filtered through celite and concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (1 × 10 mL) and dried with $MgSO_4$. The resulting crude oil was then purified by flash chromatography, eluting with 50 % EtOAc/ Pet. Ether to give desired Weinreb amide as opaque oil after concentration under reduced pressure (0.55 g, 47 % yield).

Synthesis of tosyl phenylalanine (Fig. 3) (7): To the suspension of D-phenylalanine (1 g, 6 mmol) in 25 mL water at room temperature, NaOH (0.72 g, 18 mmol) and *p*-toluene sulfonyl chloride (1.37 g, 7.2 mmol) were added[10]. The mixture was stirred at 60 °C for 6 h. Acid base washed method was used to collect product from the reaction mixture. 3M Conc. HCl and EtOAc were added to the reaction mixture. The starting material (D-phenylalanine) was protonated and shifted to the aqueous phase and product was shifted to the organic phase at pH = 1. Product was then deprotonated by adding by adding 2M NaOH aqueous solution to the organic phase and it was come back to the aqueous phase at pH =11-12. At the end, product was protonated by adding 3M HCl and was collected in organic phase. The organic phase is washed with brine, dried with $MgSO_4$ and product was obtained (1.80 g, 95 %) by evaporating the solvent.

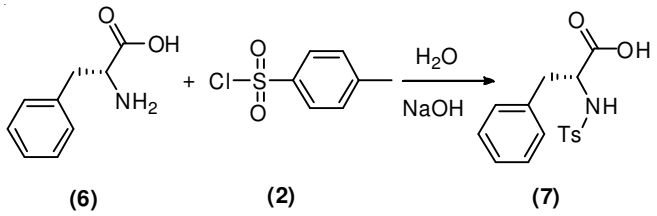


Fig. 3. Synthesis of tosyl phenylalanine

Synthesis of weinreb amide of tosyl phenylalanine (Fig. 4) (8): A solution of D-tosylphenylalanine (0.9 g, 2.5 mmol), N-methyl morpholine (0.25 g, 2.47 mmol), N,O-dimethyl-hydroxy-lamine. HCl (0.24 g, 2.46 mmol) in anhydrous CH_2Cl_2 (15 mL) is cooled to 0 °C under argon and treated with N,N-dicyclohexyl carbodiimide (0.52 g, 2.52 mmol) portion wise over 10 min[11]. The reaction mixture was stirred at 0 °C for 3 h followed by a further 15 h at room temperature, then filtered through celite and concentrated under reduced pressure. The CH_2Cl_2 (50 mL) was used to dissolve residue, washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (1 × 10 mL) and dried with $MgSO_4$. The resulting crude oil was then purified by flash chromatography, eluting with 50 % EtOAc/ Pet. Ether to give desired Weinreb amide as opaque oil after concentration under reduced pressure (0.54 g, 59 % yield).

Synthesis of dpp-alanine methyl ester hydrochloride (Fig. 5) (11): D-alanine methyl ester hydrochloride (1 g, 7.16 mmol) in anhydrous CH_2Cl_2 (18 mL, 0.4 M) was treated with

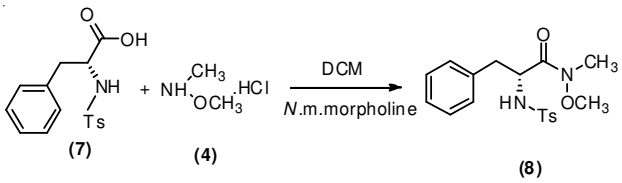


Fig. 4. Synthesis of weireb amide of phenylalanine

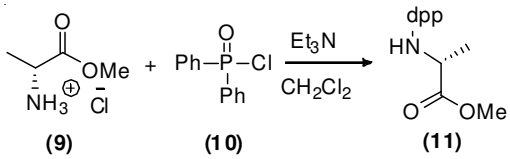


Fig. 5. Synthesis of dpp-alanine methyl ester

diphenyl phosphonic chloride (1.6 mL, 8.60 mmol) in the presence of triethyl amine (3 mL, 21.50 mmol) at 0 °C[12]. The stirring of whole reaction mixture was done at about 4 h at room temperature. Completion of the reaction mixture was determined by LC-MS. The reaction mixture was quenched with saturated aq. $NaHCO_3$ and the product was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried with $MgSO_4$. Crude product (2.07 g, 95 % yield) was obtained by evaporating dichloromethane.

Basic hydrolysis of dpp-alanine methyl ester hydrochloride (Fig. 6) (12): Dpp-alanine methylester (1 g, 3.30 mmol) was suspended in freshly distilled 1,4-dioxane (7.7 mL) and 2M sodium hydroxide (1.9 mL) was added[13]. The reaction mixture was stirred for 5 min at room temperature; colourless solution was stirred for 1 h. Consumption of the starting material was monitored by TLC. The reaction was acidified to pH 3-4 with saturated aqueous citric acid causing a white gum to separate which was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with water (1 × 50 mL), brine (2 × 50 mL) and dried with anhydrous $MgSO_4$. Evaporation of the solvent gave crude (0.93 g, 98 % yield).

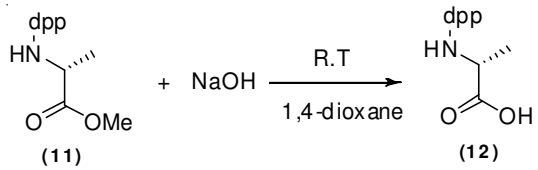
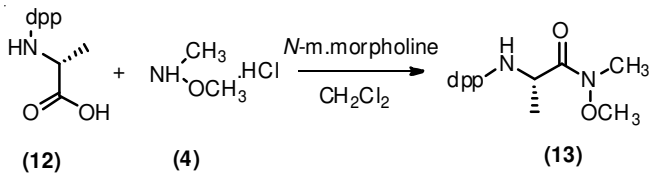


Fig. 6. Synthesis of dpp-alanine

Synthesis of weinreb amide of diphenylphosphinyl Alanine (Fig. 7) (13): A solution of dpp-alanine (1 g, 3.45 mmol), N-methyl morpholine (0.42 mL, 3.80 mmol), N,O-dimethyl-hydroxy-lamine. HCl (0.38 g, 3.80 mmol) in anhy-drous CH_2Cl_2 (14 mL) is cooled to 0 °C under argon and treated with N,N-dicyclohexyl carbodiimide (0.78 g, 3.80 mmol) portion wise over 10 min[11]. The reaction mixture was stirred at 0 °C for 3 h followed by a further 15 h at room temperature, then filtered through silica plug and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (1 × 10 mL) and dried with $MgSO_4$. The resulting crude oil was purified by flash chromatography, eluting with 5 % MeOH in DCM to give desired Weinreb amide after concentration under reduced pressure (0.47 g, 41 % yield).



(12) (4) (13)

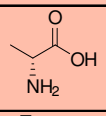
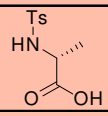
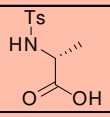
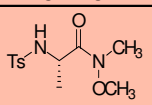
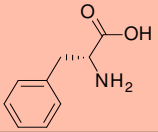
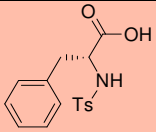
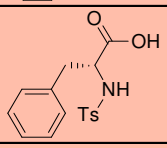
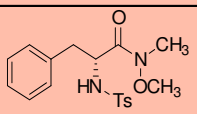
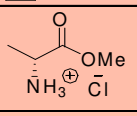
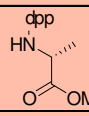
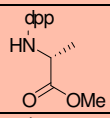
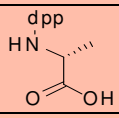
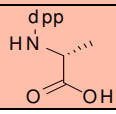
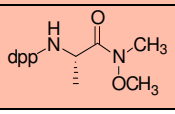
Fig. 7. Synthesis of weinreb amide

IR spectra were recorded on a Perkin-Elmer FT-IR 783 spectrophotometer. Varian NMR (400 MHz) spectrometer (model DMX 400) was used for ^{1}H NMR and ^{13}C NMR measurements. For protons, the chemical shifts were measured relative to tetramethylsilane (TMS) at $\delta = 0$ ppm.

RESULTS AND DISCUSSION

Table-1 comprises the product and their yield.

TABLE-1
PRODUCT WITH THEIR YIELDS

Entry Number	Starting Material	Product	Yield (%)
1			33
2			47
3			95
4			59
5			95
6			98
7			41

Tosyl alanine: IR (film, ν_{max}, cm^{-1}) 3270 (N-H Stretch), 3068 (sp^2 C-H Stretch), 2981(sp^3 C-H Stretch), 1710 (C=O Stretch), 1423 (C=C Stretch), 1340 (C-N Stretch), 678 (CH bending). δ_H (300 MHz; $CDCl_3$) 9.39 (1 H, s, COO*H*), 7.73 (2 H, d, *J* 8.3,Ar*H*), 7.28 (2 H, d, *J* 8.3, Ar*H*), 5.35-5.38 (1 H, d, *J* 8.3, NH), 3.95-4.05 (1 H, dq, *J* 7.2, 8.3, CH), 2.41 (3 H, s, $ArCH_3$), 1.40 (3 H, d, *J* 7.2, CH_3). δ_C (75 MHz; $CDCl_3$) 177.1 (CO), 144.1 (C), 136.8 (C), 129.9 (ArCH), 127.3 (ArCH), 51.2 (CH), 21.6 ($ArCH_3$), 19.7 (CH_3).
R_f 0.30 (EtOAC-P.E, 50:50).

Winreb amide of tosyl alanine: IR (film, ν_{max}, cm^{-1}) 3260 (N-H Stretch), 2978 (sp^3 C-H Stretch), 1651 (C=O Stretch), 1416 (C=C Stretch), 1331 (C-N Stretch), 1152 (C-O Stretch), 665 (CH bending). δ_H (300 MHz; $CDCl_3$) 7.69 (2 H, d, *J* 8.3 ArH), 7.23-7.26 (2 H, m, ArH), 5.63 (1 H, d, *J* 9.3, NH), 4.26-4.36 (1 H, dq, *J* 6.9, 9.3, CH), 3.52 (3 H, s, OCH_3), 2.96 (3 H, s, CH_3), 2.37 (3 H, s, $ArCH_3$), 1.27 (3 H, d, *J* 6.9, CH_3). δ_C (75 MHz; $CDCl_3$) 172.4 (CO), 143.5 (C), 137.2 (C), 129.6 (ArCH), 127.4 (ArCH), 127.2 (CH), 61.5 (OCH_3), 48.9 (CH_3), 21.6 ($ArCH_3$), 20.0 (CH_3). R_f 0.24 (EtOAC-P.E, 50:50).

Tosyl phenylalanine: IR (film, ν_{max}, cm^{-1}) 3321 (N-H Stretch), 3030 (sp^2 C-H Stretch), 2925(sp^3 C-H Stretch), 1710 (C=O Stretch), 1455 (C=C Stretch), 1330 (C-N Stretch), 684 (CH bending). δ_H (300 MHz; $CDCl_3$) 7.59 (2 H, d, *J* 8.3, Ar*H*), 7.20-7.26 (5 H, m, Ar*H*), 7.06-7.09 (2 H, m, Ar*H*), 5.00 (1 H, d, *J* 8.6, NH), 4.18-4.24 (1 H, ddd, *J* 11.7, 8.6,5.6, CH), 3.07-3.13 (1 H, dq, *J* 13.7, 5.6, -ArC*H*HCH), 2.97-3.04 (1 H, dq, *J* 13.7, 5.6, -ArCH*H*CH), 2.41 (3 H, s, $ArCH_3$). δ_C (75 MHz; $CDCl_3$) 173.1 (CO), 143.2 (C), 137.7 (C), 136.5 (C), 129.2 (ArCH), 128.1 (ArCH), 126.8 (ArCH), 126.6 (ArCH), 57.5 (CH), 38.7 (CH_2), 20.3 ($ArCH_3$). R_f 0.23 (EtOAC-P.E, 50:50).

Weinreb amide of tosyl phenylalanine: IR (film, ν_{max}, cm^{-1}) 3236 (N-H Stretch), 2928 (sp^3 C-H Stretch), 1647 (C=O Stretch), 1454 (C=C Stretch), 1331 (C-N Stretch), 1155 (C-O Stretch), 665 (CH bending). δ_H (300 MHz; $CDCl_3$) 7.60 (2 H, d, *J* 8.2, Ar*H*), 7.07-7.26 (7 H, m, Ar*H*), 5.56-5.59 (1 H, d, *J* 9.6, NH), 4.48-4.55 (1 H, dt, *J* 13.3, 9.6, 7.0, CH), 3.40 (3 H, s, OCH_3), 2.95-2.99 (1 H, dd, *J* 13.3, 7.5, -ArC*H*HCH), 2.93 (3 H, s, CH_3), 2.81-2.86 (1 H, dd, *J* 13.3, 7.5, -ArCH*H*CH), 2.36(3 H, s, $ArCH_3$). δ_C (75 MHz; $CDCl_3$) 171.3 (CO), 143.4 (C), 137.0 (C), 135.9 (C), 129.7 (ArCH), 128.5 (ArCH), 127.3 (ArCH), 127.01 (ArCH), 61.4 (CH), 54.2 (CH_2), 39.8 (OCH_3), 32.2 (CH_3), 21.6 ($ArCH_3$). R_f 0.32 (EtOAC-Pet.Ether, 50:50). m.p around room temperature; *m/z* (ESI) 362 ; HRMS (ESI) calcd for $C_{18}H_{22}N_2O_4S$; $C_{18}H_{22}N_2O_4SNa^+$ 385.11 Mass analysis for mass 385.1181000 and found to be 385.1192490.

dpp-Alanine methyl ester hydrochloride: IR (film, ν_{max}, cm^{-1}) 3166 (N-H Stretch), 2987(sp^2 C-H Stretch), 2880(sp^3 C-H Stretch), 1737 (C=O Stretch), 1454 (C=C Stretch), 1331 (SO_2 Stretch), 1155 (SO_2 Stretch), 721 (P=O Stretch), 665 (CH bending). δ_H (400 MHz; $CDCl_3$) 7.73-7.91 (5 H, m, ArH), 7.41-7.49 (5 H, m, ArH), 4.06-4.13 (1 H, dq, *J* 14.4, 6.8, CH_3CHNH-), 3.91 (1H, d, *J* 6.8, CH_3CHNH-), 3.69 (3 H, s, CH_3O-), 1.42 (3 H, d, *J* 6.8, CH_3CHNH-); δ_C (100 MHz; $CDCl_3$) 174.6 (-CO), 132.8-133.4 (m, ArC), 131.9-132.3 (m, ArC), 131.2-131.7 (m, ArC), 128.5-128.7 (dd, *J* 12.7, 4, ArC), 52.5 (-OCH_3), 49.3 (CH_3CHNH-), 22.0 (CH_3CHNH-), R_f 0.18 (EtOAC-P.E, 50:50).

dpp-Alanine: IR (film, ν_{max}, cm^{-1}) 3343(-OH Stretch), 3060 (N-H Stretch), 2973(sp^2 C-H Stretch), 2876(sp^3 C-H Stretch), 1723 (C=O Stretch), 1438 (C=C Stretch), 1284 (SO_2 Stretch), 1123 (SO_2 Stretch), 726 (P=O Stretch), 691 (CH bending). δ_H (400 MHz; $CDCl_3$) 9.8 (1 H, br. s, -OH), 7.84-7.96 (4 H, m, ArH), 7.40-7.57 (6 H, m, ArH), 3.90 (d, *J* 5.1 Hz, CH_3CHNH-), 3.78-3.85 (1 H, m, CH_3CHNH-), 1.39 (3 H, d, J 6.8, CH_3CHNH-), δ_C (100 MHz; $CDCl_3$) 175.2 (-CO), 132.9-133.2 (m, ArC), 132.4-132.7 (m, ArC), 131.5-131.7 (m, ArC), 128.6-128.8 (dd, *J* 13.2, 5.5, ArC), 49.6 (CH_3CHNH-), 21.3 (CH_3CHNH-), R_f 0.46 (EtOAC-P.E, 9:1).

Weinreb amide of diphenylphos-phinyl alanine: IR (film, ν_{max}, cm^{-1}) 3269 (N-H Stretch), 3057(sp^2 C-H Stretch), 2979 (sp^3 C-H Stretch), 1654 (C=O Stretch), 1438 (C=C Stretch), 1384 (SO_2 Stretch), 1195 (SO_2 Stretch), 724 (P=O

Stretch), 698 (CH bending). δ_H (400 MHz; $CDCl_3$) 7.82-7.93 (4 H, m, ArH), 7.38-7.51 (6 H, m, ArH), 4.18-4.28 (1 H, m, CH_3CHNH-),3.94-3.99 (1H, t, *J* 10.3, CH_3CHNH-), 3.37 (3 H, s,-$NOCH_3$), 3.14 (3 H, s, -NCH_3), 1.36 (3 H, d, *J* 6.8, CH_3CHNH-), δ_C (100 MHz; $CDCl_3$) 174.4 (-CO), 133.0-133.4 (m, ArC), 132.1-132.4 (m, ArC), 131.7-131.9 (m, ArC), 128.4-128.6 (dd, *J* 12.5, 1.6, ArC), 61.2 (CH_3CHNH-), 46.3 (-$NOCH_3$), 32.0 (-NCH_3), 21.8 (CH_3CHNH-), R_f 0.41 (MeOH-DCM, 5:95); m.p. 89-90 °C; *m/z* (ESI) 332.13; HRMS (ESI) calcd. for $C_{17}H_{21}N_2O_3PH^+$ 332.13, found 333.13; $C_{17}H_{21}N_2O_3PNa^+$ 335.11 Mass analysis for mass 355.1174520 and found to be 355.1182002.

Three different Weinreb amides were prepared **5**, **8** and **13** by using different protecting groups and excellent results were obtained. In synthesize of Weinreb amides -NH_2 group was protected in amino acids. Since amino acids and alcohols have poor leaving groups in SN^2 reactions. This is the reason for tosylate group must be introduced. Since -OTs group can be deprotected easily in acidic media so tosylamines are converted into corresponding Weinreb amides **5**,**8**.

In order to synthesize dpp-protected Weinreb amide **13**, amino group is protected with -dpp protecting group. This protection was not stable in strong acidic media. In work up of Weinreb amide **13**, celite was used in filtration, most of the product remained in celite and deprotected due to its acidic nature. EtOAc, Petroleum ether (1:1) system could not elute product from celite. Second time product was filtered through silica plug and MeOH, DCM (5:95) system was used to elute the product.

Conclusion

Diphenyl phosphinic chloride (dpp-) protection was stable to bases and catalytic hydrogenation but sensitive to acids. It is clear from above results that yield of -dpp protected Weinreb amide is low as compared to -OTs protected Weinreb amides. This is due to the large steric bulk of -dpp group than -OTs group. Similarly some amount of -dpp protected Weinreb amide was decomposed during product purification.

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