

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 (-NH₂) 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 Nahm¹ 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 synthesis². 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 aldehydes³ and α -amino ketones⁴. Most direct conversions of carboxylic acids into the corresponding Weinreb amides have utilized peptide-coupling reagents such as benzotriazol-1-yl-N-oxy-tris- (dimethyl-amino) phosphonium hexafluorophosphate (BOP)⁵ N,N'-dicyclohexylcarbodiimide (DCC)⁶ or propylphosphonic anhydride/N-ethyl morpholine⁷.

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 -NH₂ protection and -OH protection in amino acids and amino alcohols. Tosylamine is the intermediate, when -NH₂ 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 -NH₂ 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 added¹⁰. 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 %).

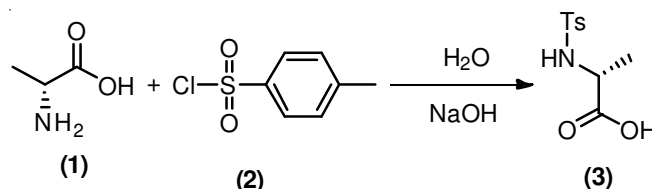


Fig. 1. Synthesis of tosylalanine

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 CH₂Cl₂ (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 min¹¹. Stirring was done at 0 °C for 3 h followed by a

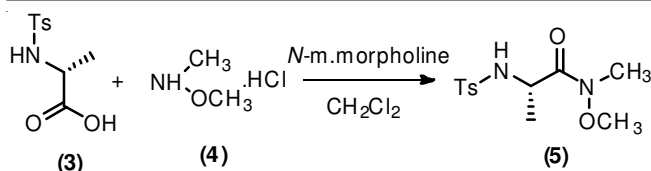


Fig. 2. Synthesis of weinreb amide

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 added¹⁰. 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.

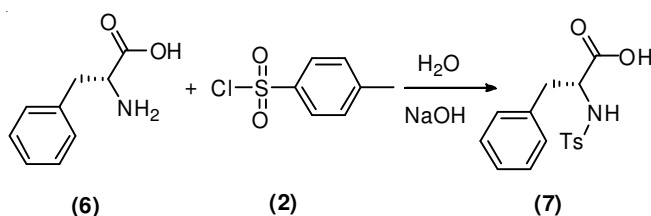


Fig. 3. Synthesis of tosyl phenylalanine

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-dimethylhydroxy-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 min¹¹. 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

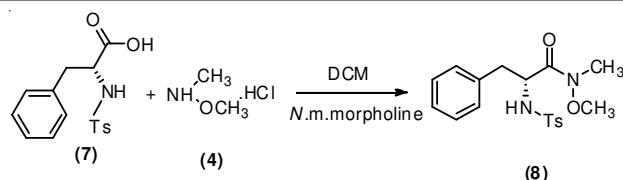


Fig. 4. Synthesis of weinreb amide of phenylalanine

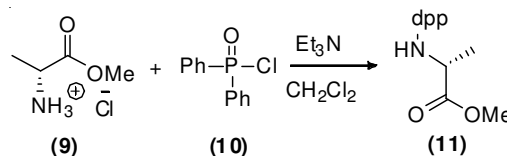


Fig. 5. Synthesis of dpp-alanine methyl ester

diphenyl phosphonic chloride (1.6 mL, 8.60 mmol) in the presence of triethyl amine (3 mL, 21.50 mmol) at 0 °C¹². 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 added¹³. 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).

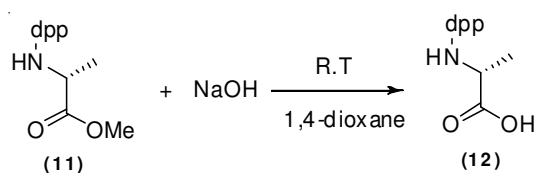


Fig. 6. Synthesis of dpp-alanine

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-dimethylhydroxy-lamine. HCl (0.38 g, 3.80 mmol) in anhydrous 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 min¹¹. 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).

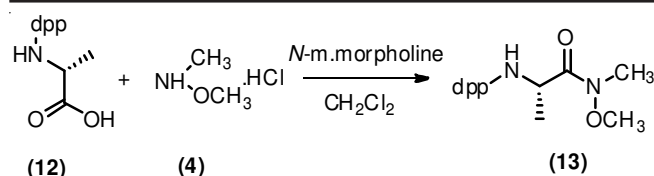


Fig. 7. Synthesis of weinreb amide

IR spectra were recorded on a Perkin-Elmer FT-IR 783 spectrophotometer. Varian NMR (400 MHz) spectrometer (model DMX 400) was used for ^1H 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, $\nu_{\max}$, 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, COOH), 7.73 (2 H, d, J 8.3, ArH), 7.28 (2 H, d, J 8.3, ArH), 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, ArCH₃), 1.40 (3 H, d, J 7.2, CH₃). 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 (ArCH₃), 19.7 (CH₃). R_f 0.30 (EtOAC-P.E, 50:50).

Winreb amide of tosyl alanine: IR (film, $\nu_{\max}$, 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, OCH₃), 2.96 (3 H, s, CH₃), 2.37 (3 H, s, ArCH₃), 1.27 (3 H, d, J 6.9, CH₃). 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 (OCH₃), 48.9 (CH₃), 21.6 (ArCH₃), 20.0 (CH₃). R_f 0.24 (EtOAC-P.E, 50:50).

Tosyl phenylalanine: IR (film, $\nu_{\max}$, 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, ArH), 7.20-7.26 (5 H, m, ArH), 7.06-7.09 (2 H, m, ArH), 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, -ArCHHCH), 2.97-3.04 (1 H, dq, J 13.7, 5.6, -ArCHHCH), 2.41 (3 H, s, ArCH₃). 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 (CH₂), 20.3 (ArCH₃). R_f 0.23 (EtOAC-P.E, 50:50).

Weinreb amide of tosyl phenylalanine: IR (film, $\nu_{\max}$, 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, ArH), 7.07-7.26 (7 H, m, ArH), 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, OCH₃), 2.95-2.99 (1 H, dd, J 13.3, 7.5, -ArCHHCH), 2.93 (3 H, s, CH₃), 2.81-2.86 (1 H, dd, J 13.3, 7.5, -ArCHHCH), 2.36 (3 H, s, ArCH₃). 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 (CH₂), 39.8 (OCH₃), 32.2 (CH₃), 21.6 (ArCH₃). R_f 0.32 (EtOAC-Pet.Ether, 50:50). m.p around room temperature; m/z (ESI) 362; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$; $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4\text{SNa}^+$ 385.11 Mass analysis for mass 385.1181000 and found to be 385.1192490.

dpp-Alanine methyl ester hydrochloride: IR (film, $\nu_{\max}$, 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 (SO₂ Stretch), 1155 (SO₂ 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, CH₃CHNH-), 3.91 (1H, d, J 6.8, CH₃CHNH-), 3.69 (3 H, s, CH₃O-), 1.42 (3 H, d, J 6.8, CH₃CHNH-); 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 (-OCH₃), 49.3 (CH₃CHNH-), 22.0 (CH₃CHNH-), R_f 0.18 (EtOAC-P.E, 50:50).

dpp-Alanine: IR (film, $\nu_{\max}$, 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 (SO₂ Stretch), 1123 (SO₂ 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, CH₃CHNH-), 3.78-3.85 (1 H, m, CH₃CHNH-), 1.39 (3 H, d, J 6.8, CH₃CHNH-), 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 (CH₃CHNH-), 21.3 (CH₃CHNH-), R_f 0.46 (EtOAC-P.E, 9:1).

Weinreb amide of diphenylphos-phenyl alanine: IR (film, $\nu_{\max}$, 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 (SO₂ Stretch), 1195 (SO₂ 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, $\text{CH}_3\text{CHNH-}$), 3.94-3.99 (1H, t, J 10.3, $\text{CH}_3\text{CHNH-}$), 3.37 (3 H, s, $-\text{NOCH}_3$), 3.14 (3 H, s, $-\text{NCH}_3$), 1.36 (3 H, d, J 6.8, $\text{CH}_3\text{CHNH-}$), δ_{C} (100 MHz; CDCl_3) 174.4 ($-\text{CO}$), 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 ($\text{CH}_3\text{CHNH-}$), 46.3 ($-\text{NOCH}_3$), 32.0 ($-\text{NCH}_3$), 21.8 ($\text{CH}_3\text{CHNH-}$), R_f 0.41 (MeOH-DCM, 5:95); m.p. 89-90 °C; m/z (ESI) 332.13; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_3\text{PH}^+$ 332.13, found 333.13; $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_3\text{PNa}^+$ 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 synthesis of Weinreb amides $-\text{NH}_2$ 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 $-\text{OTs}$ 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 $-\text{dpp}$ 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 $-\text{dpp}$ protected Weinreb amide is low as compared to $-\text{OTs}$ protected Weinreb amides. This is due to the large steric bulk of $-\text{dpp}$ group than $-\text{OTs}$ group. Similarly some amount of $-\text{dpp}$ protected Weinreb amide was decomposed during product purification.

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REFERENCES

1. S. Nahm and S.M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).
2. (a) M.P. Sibi, *Org. Prep. Proced. Int.*, **25**, 15 (1993).; (b) M. Mentzel and H.M.R.J. Hoffmann, *J. Prakt. Chem.*, **339**, 517 (1997).; (c) J. Singh, N. Satyamurthi and I.S. Aidhen, *J. Prakt. Chem.*, **342**, 340 (2000).
3. J. Jurczak and A. Golebiowski, *Chem. Rev.*, **89**, 149 (1989).
4. J. M. Hamby and J. C. Hodges, *Heterocycles*, **35**, 843 (1993).
5. I. Maugras, J. Poncet and P. Jouin, *Tetrahedron*, **46**, 2807 (1990).
6. M. Braun and D. Waldmüller, *Synthesis*, 856 (1989).
7. W. Oppolzer and A.F. Cunningham, *Tetrahedron Lett.*, **27**, 5467 (1986).
8. T.W. Green and P.G.M. Wuts, *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York (1999).
9. P.J. Kocienski, *Protecting Groups*; Georg Thieme Verlag: Stuttgart-New York (2004).
10. S.B. Sdira, C.P. Felix, M.-B.A. Giudicelli, P.F. Seigle-Ferrand, M. Perrin and R.J. Lamartine, *J. Org. Chem.*, **68**, 6632 (2003).
11. Z.H. Zhou, Y.L. Tang, K.Y. Li, B. Liu and C.C. Tang, *Heteroatom Chem.*, **14**, 603 (2003).
12. P.G.M. Wuts, *Greene's Protective Groups in Organic Synthesis*, edn 3 (1998).
13. R. Ramage, D. Hopton, M.J. Parrott, G.W. Kenner and G.A. Moore, *J. Chem. Soc., Perkin Trans. 1*, 1357 (1984).