

Synthesis of β -Amido Phosphine Oxides and N-(1-oxo-2-diphenylphosphinoyl) Ethyl-4-substituted-2-oxazolidinones by using Arbusov Reaction

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A number of α -amino-acids (**8a-c**) have been used as precursors to prepare the corresponding 4-substituted-2-oxazolidinones (**9a-c**). N-chloroacetylation of these oxazolidinones followed by the reaction of Michaelis-Arbusov rearrangement using methoxy diphenyl phosphine provides an efficient and simple method for preparing optically active β -amido-phosphine oxides (**5a-c**) and N-(1-oxo-2-diphenylphosphinoyl) ethyl-4-substituted-2-oxazolidinones (**6a-c**) in good overall yields.

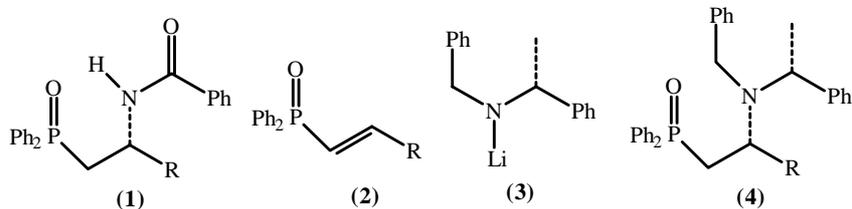
Key Words: Phosphine oxides, Arbusov reaction.

INTRODUCTION

In recent years a number of papers are present in literature describing the synthesis and application of phosphine oxides¹⁻⁷. The diphenyl phosphinoyl group is a powerful stereodirecting group which can be used to control relative and absolute stereochemistry as well as double bond geometry¹. Furthermore it is known that phosphorus substituents regulate important biological functions⁸. The presence of functional group such as amido group in phosphine oxides has been reported to be the precursors of allylic amides⁹, allylic alcohols¹⁰, alkynyloxazolidinone¹¹ and allylic sulfides¹², with 1,4-related chiral centres across double bond. β -Amidophosphine oxides have also been established as intermediates in the synthesis of optically active cyclopropyl ketones^{13,14}.

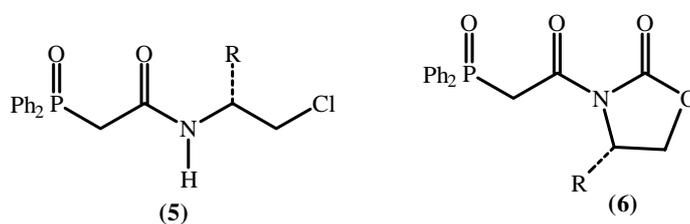
In 1993, Worren and co-workers¹³ describe how β -functionalized phosphine oxides (**1**) can be synthesized by treatment of the vinyl phosphine oxides (**2**) with the lithium amide (**3**)¹⁵, chloro methylsilane^{16,17} and tetra *n*-butyl ammonium fluoride (TBAF), respectively. The resulting α -aminophosphine oxides (**4**) reduced by H₂.Pd/C and then treated with 2-methoxy-2-phenyl acetic acid, DCC and cat. DMAP (Fig. 1).

In this paper we describe the preparation of novel chiral N-(2-chloro-1-substituted)diphenylphosphinoylacetamide (**5a-c**) and N-(1-oxo-2-diphenyl phosphinoyl)ethyl-4-substituted-2-oxazolidinone (**6a-c**) by using Arbusov reaction (Fig. 2).



a: R = Ph, b: *p*-MeOC₆H₄, c: R = 2-Furyl

Fig.1



a: R = H, b: R = Ph, c: R = Benzyl

Fig.2

EXPERIMENTAL

All 300 MHz ¹H and 75 MHz ¹³C NMR spectra were run on a Burkert AC 300 spectrometer; 200 MHz NMR spectra were run on a Bruker AC 200 NMR spectrometer. ¹³C NMR spectra were recorded using distortionless enhancement by polarisation transfer. Both NMR spectra were recorded using CHCl₃ as internal standard. Fast atom bombardment (FAB) were recorded with a Kratos MS 50 with a *m*-nitrobenzylalcohol matrix. Accurate mass determinations were carried out on a Kratos MS 50 concept IS spectrometer. Elemental analysis were performed using a Carlo-Erba 1106 elemental analyser. Infrared spectra were recorded using a Perkin-Elmer 783 spectrometer equipped with a PE 600 data station. Melting points were determined using an Electrothermal melting point apparatus and were uncorrected. Column chromatography was conducted on precoated aluminium sheets (60 F 254) with a 0.2 mm thickness (Aldrich chemical co.).

Preparation of (S)-(+)-(N-chloroacetyl)-4-benzyl-2-oxazolidinone (10c): A dry 250 mL flask equipped with a magnetic stirring bar is charged with 5.0 g (28.3 mmol) of S-(+)-(benzyl)-2-oxazolidinone, capped with a rubber septum and flushed with nitrogen. Anhydrous tetrahydrofuran (85 mL) is then added to the flask *via* cannula and the resulting solution of 11.3 mL (28.25 mmol) of 2.5 M butyllithium in hexane was added dropwise *via* a syringe. The solution was turned slightly cloudy. Freshly chloroacetylchloride (3.51 g, 31.07 mmol) is added in one portion by syringe after completion of the addition. The resulting clear, nearly

colourless solution is stirred for 0.5 h period. Excess chloroacetylchloride is quenched by the addition of 20 mL of saturated aqueous ammonium chloride. The bulk of the tetrahydrofuran and hexane is removed on a rotavapor (bath temperature *ca.* 40-50°C) and the resulting slurry is extracted with two 50 mL portions of CH₂Cl₂. The combined organic extracts were dried over anhydrous magnesium sulphate and filtered. The solvent is removed by rotavapor and the residue, light yellow oil, is placed in refrigerator overnight to crystallize. The resulting crystalline solid is pulverised and triturated with a minimum quantity of cold diethyl ether. After filtration and drying (6.8 g, 95%) of (S)-(+)-(N-chloroacetyl)-4-benzyl-2-oxazolidine was obtained as a colourless crystalline solid, mp 172-174°C. The product showed a rotation of $[\alpha]_D^{25} +96$ (c 1.0, CHCl₃) and has the following spectroscopic properties:

Spectroscopic data for (N-chloroacetyl)-2-oxazolidine (10a): mp 56-58°C, ¹H NMR (CDCl₃): δ 4.06 (2H, pseudo t, J = 8.4, 7.8 Hz, CH₂O), 4.48 (2H, pseudo t, J = 8.3, 7.9 Hz, CH₂N), 4.70 (2H, s, CH₂Cl). ¹³C NMR (CDCl₃): δ 42.74 (CH₂O), 43.69 (CH₂N), 63.23 (CH₂Cl), 153.65 (CO), 166.23 (CO, carbonyl). IR (KBr, ν_{\max} , cm⁻¹): 1770 (C=O), 1710 (C=O), 1230 (CH₂Cl), 1215 (C-O). m/s (FAB) 289 [(2M+HCl)⁺, 18], 176 (7), 166 (15), 165 (7), (MH⁺, 83), 136 [(M-CO)⁺, 100], 123 (8), 105 (10), 91 (18). Anal. calcd. for C₅H₆NO₃Cl: C, 36.7; H, 3.7; N, 8.6; Cl, 21.7. Found : C, 36.9; H, 3.6; N, 8.6; Cl, 21.4.

Spectroscopic data of (S)-(+)-(N-chloroacetyl)-4-phenyl-2-oxazolidine (10b): mp 113°C, $[\alpha]_D^{25} -89$ (c 1.0, CHCl₃), ¹H NMR (CDCl₃): δ 4.12-4.17 (1H, dd, J = 9.0, 4.0 Hz, HCHO), 4.65-4.85 (1H, dd, J = 9.0, 4.0 Hz, HCHO), 4.70 (2H, s, CH₂Cl), 5.45 (1H, dd, J = 9.0, 4.0, PhCH), 7.26-7.60 (5H, m, Ar-H). ¹³C NMR (CDCl₃): δ 43.74 (CH₂Cl), 57.56 (CH), 70.82 (CH₂O), 126.15 (CH, Ar), 129.12 (CH, Ar), 129.33 (CH), 129.99 (CH, Ar), 138.07 (C, Ar), 153.49 (CO, carbonyl), 165.53 (CO, carbonyl). IR (KBr, ν_{\max} , cm⁻¹): 1775 (C=O), 1350 (CH₂Cl), 1215 (C-O). m/z (FAB) 240 (MH⁺, 100).

Spectroscopic data of (S)-(+)-(N-chloroacetyl)-4-benzyl-2-oxazolidine (10c): ¹H NMR (CDCl₃): δ 2.81 (1H, dd, J = 13.4, 9.5 Hz, HCHO), 3.34 (1H, dd, J = 13.4, 3.2 Hz, HCHO), 4.2 (1H, dd, J = 9.3, 3.4 Hz, HCHPh), 4.32 (1H, pseudo t, J = 9.2 Hz, HCHPh), 4.70 (1H, ddd, J = 10.7, 7.4, 3.7 Hz, CHN), 4.80 (2H, s, CHCl), 7.20-7.38 (5H, m, Ar-H). ¹³C NMR (CDCl₃): δ 37.52 (CH₂Cl), 43.92 (CH₂O), 55.49 (CH), 77.16 (PhCH₂), 127.64 (CH), 129.16 (CH), 129.33 (CH), 130.99 (CH), 134.79 (C), 153.30 (CO), 166.17 (CO), 166.17 (CO). IR (KBr, ν_{\max} , cm⁻¹): 1770 (C=O), 1360 (CH₂Cl), 1215 (C-O). m/s (FAB) 507 [(2M+H)⁺, 5], 307 (7), 257 (4), 256 (42), 255 (30), 254 (MH⁺, 100), 289 (M+Cl)⁺, 7), 178 [(M-COCHCl)⁺, 10], 154 (23), 137 (24), 117 (43), 91 (77). Anal. calcd for C₁₂H₁₂NO₃Cl: C, 56.8; H, 4.7; N, 5.5; Cl, 14.0. Found: C, 56.9; H, 4.9; N, 5.5; Cl, 14.1.

Preparation and spectroscopic data of methoxy diphenylphosphine (11): Methanol (9.2 mL, 22.7 mmol) and N,N-dimethylaniline (2.88 mL, 22.7 mmol) were stirred in diethyl ether (10 mL) in an ice bath and under nitrogen atmosphere. Chlorodiphenylphosphine (4.07 mL, 22.7 mmol) was added drop wise. Almost immediately after the end of addition of the phosphine, a precipitate formed. The reaction was stirred for 1.5 h after which the N, N-dimethylaniline hydrochloride was filtered off and washed with ether. The combined filtrate and washing were distilled under vacuum to yield colourless liquid. Bp 140-143°C (8 mm Hg); ¹H NMR (CDCl₃): δ 3.65 (3H, d, J_{PH} = 14.0 Hz, POCH₃) 7.20-7.90 (10 H, m, Ar-H). ¹³C NMR (CDCl₃): δ 56.88 (d, J_{PC} = 19.0 Hz, CH₃), 128.46 (d, J_{PC} = 7 Hz, CH), 129.61 (CH), 130.49 (d, J_{PC} = 22 Hz, CH), 141.57 (d, J_{PC} = 19 Hz, C). IR (KBr, ν_{max}, cm⁻¹): 1040 (P-OMe). m/z (FAB) 995 (37), 387 (35), 338 (11), 233 (10), 217 (MH⁺, 100), 183 (57), 165 (17), 155 (33), 136 (16), 91 (18).

Synthesis of 5c and 6c: A dry path distillation apparatus having a septum in place of a thermometer was filled with N₂ and charged with methanol (0.46 mL, 11.35 mmol), N, N'-dimethylaniline (1.44 mL, 11.35 mmol) and diethyl ether (10 mL) at 0°C. Chlorodiphenylphosphine (2.04 mL, 11.35 mmol) was added dropwise *via* a syringe. Almost immediately after the end of the addition of phosphine, a precipitate formed. After stirring at 0°C for 1.5 h (S)-(-)-4-benzyl-3-(2-chloro-1-oxoethyl)-2-oxazolidine (1.86 g, 11.35 mmol) in anhydrous THF (40 mL) was added and the septum was replaced with a thermometer and a mixture of THF and diethyl ether was removed by distillation at 1 atm (N₂). The mixture was cooled and the still head was replaced with a reflux condenser fitted with a septum with maintenance of the N₂ atmosphere. The mixture was heated gently at 80°C for 0.5 h, then at 150°C (oil bath temperature) for 2 h. After cooling, the yellow oil was subjected to column chromatography on silica gel.

Spectroscopic data of N-(2-chloroethyl) diphenylphosphinoylacetamide (5a): (3.04 g, 7.38 mmol, 65%; CH₂Cl₂/CHCl₃ were used as eluent) obtained as a white solid after recrystallization from ethyl acetate: ¹H NMR (CDCl₃): δ 2.08 (1H, brs, NH), 3.25 (2H, d, J_{PH} = 12.5 Hz, CH₂PO), 3.40-3.55 (4H, CH₂CH₂Cl), 7.26-7.82 (10H, m, Ar-H). ¹³C NMR (CDCl₃): δ 38.65 (d, J_{PC} = 54.0 Hz, OPCH₂), 41.51 (CH₂N), 42.78 (CH₂Cl), 128.80 (d, J_{PC} = 12.0 Hz, CH), 130.72 (d, J_{PC} = 10.0 Hz, CH), 131.99 (C), 132.39 (d, J_{PC} = 3.0 Hz, CH), 165.08 (d, J_{PC} = 4.0 Hz, CO), 137.14 (C). IR (KBr, cm⁻¹): 3260-3060 ν(NH), 1185 ν(P=O). m/z (FAB) 325 (7), 324 (38), 323 (23), 322 (MH⁺, 100), 202 (Ph₂POH⁺, 18), 201 (Ph₂PO⁺, 80), 183 (5), 154 (6). Anal. calcd. for C₁₆H₁₇N₂OPCl: C, 59.7; H, 5.3; N, 4.3; P, 9.6. Found: C, 59.6; H, 5.2; N, 4.4; P, 9.4.

(S)-(+)-N-(2-chloro-1-benzylethyl) diphenylphosphinoylacetamide (5c): (3.04 g, 7.38 mmol, 65%; CH₂Cl₂/CHCl₃ were used as eluent)

obtained as a white solid after recrystallization from ethyl acetate: $[\alpha]_D + 15^\circ$ (cl, CHCl_3); mp 172-174°C. ^1H NMR (CDCl_3): δ 2.15 (1H, brs, NH), 2.75 (1H, dd, $J = 13.8, 6.8$ Hz, HCHPh), 2.87 (1H, dd, $J = 13.6, 7.8$ Hz, HCHPh), 3.31 (1H, overlapping, HCHC), 3.33 (2H, d, $J_{\text{PH}} = 12.7$ Hz, CH_2PO), 3.38 (1H, ddd, $J = 20.3, 11.2, 4.3$ Hz, HCHCl), 4.32 (1H, pseudo dd, $J = 6.9, 3.2$ Hz, CH), 7.18-7.85 (15H, m, Ar-H). ^{13}C NMR (CDCl_3): δ 37.53 (PhCH_2), 38.72 (d, $J_{\text{PC}} = 60.0$ Hz, PCH_2), 41.50 (CH), 46.21 (CH_2Cl), 126.88 (CH), 128.19 (d, $J_{\text{PC}} = 13.0$ Hz, CH), 129.04 (d, $J_{\text{PC}} = 7.4$ Hz, CH), 129.11 (d, $J_{\text{PC}} = 4.1$ Hz, CH), 130.95 (d, $J_{\text{PC}} = 10.0$ Hz, CH), 132.62 (CH), 137.14 (C), 164.64 (CO). IR (KBr, ν_{max} , cm^{-1}): 3250-3060 ($\nu(\text{NH})$), 1660 ($\nu(\text{C}=\text{O})$), 1325 ($\nu(\text{CH}_2\text{Cl})$), 1185 ($\nu(\text{P}=\text{O})$). m/z (FAB) 415 (7), 414 (41), 413 (25), 415 (MH^+ , 100), 243 ($\text{Ph}_2\text{POCH}_2\text{CHO}^+$, 23), 201 (PH_2PO^+ , 96), 154 (85), 91 (56). Anal. calcd. for $\text{C}_{23}\text{H}_{23}\text{NO}_2\text{PCl}$: C, 67.1; H, 5.6; N, 3.4; P, 7.5. Found: C, 66.8; H, 5.8; N, 3.2; P, 7.5.

Spectroscopic data of (1-oxo-2-diphenylphosphinoyl)ethyl-2-oxazolidinone (6a): (0.6 g, 1.48 mmol, 13%; acetone was used as eluent) obtained as a white solid after recrystallization from ethyl acetate. mp 176-178°C. ^1H NMR (CDCl_3): δ 3.88 (2H, pseudo t, $J = 8.1, 7.9$ Hz, CH_2O), 4.24 (2H, pseudo t, $J = 8.2, 7.2$ Hz, CH_2N), 4.32 (2H, d, $J_{\text{PH}} = 14.1$ Hz, CH_2PO), 7.26-2.83 (10H, m, Ar-H). ^{13}C NMR (CDCl_3): δ 37.60 (PhCH_2), 38.12 (d, $J_{\text{PC}} = 59.00$ Hz, PCH_2), 55.57 (CH), 66.01 (CH_2O), 127.17 (CH), 128.65 (d, $J_{\text{PC}} = 25.0$ Hz, CH), 129.05 (d, $J_{\text{PC}} = 7.4$ Hz, CH), 130.99 (CH), 131.00 (d, $J_{\text{PC}} = 10.0$ Hz, CH), 132.37 (CH), 136.36 (C), 153.54 (CO), 165.28 (d, $J_{\text{PC}} = 6.4$ Hz, CO). IR (KBr, ν_{max} , cm^{-1}): 1660 ($\text{C}=\text{O}$), 1440 (C-N), 1185 ($\text{P}=\text{O}$). m/z (FAB) 329 (MH^+ , 100), 243 ($\text{Ph}_2\text{POCH}_2\text{CHO}^+$, 80), (PH_2PO^+ , 70).

Spectroscopic data of (S)-(+)-(1-oxo-2-diphenylphosphinoyl)ethyl-4-phenyl-2-oxazolidinone (6b): (0.37 g, 0.91 mmol, 23%) obtained as a white solid after recrystallization from ethyl acetate: $[\alpha]_D + 65^\circ$ (cl, CHCl_3). ^1H NMR (CDCl_3): δ 4.11-4.19 (2H, M, CH_2O), 4.44 (1H, pseudo t, $J_{\text{PH}} = 13.5$ Hz, HCHPO), 4.54 (1H, dd, $J_{\text{PH}} = 14.7, J_{\text{HH}} = 13.5$ Hz, HCHPO), 4.55 (1H, dd, CH), 7.21-7.83 (15H, m, Ar-H). ^{13}C NMR (CDCl_3): δ 37.80 (d, $J_{\text{PC}} = 59.00$ Hz, PCH_2), 58.0 (CH), 69.9 (CH_2), 128.60-132.30 [3 (CH) and 3 C, Ar], 138.00 (CO), 153.80 (CO). IR (KBr, ν_{max} , cm^{-1}): 1790 ($\text{C}=\text{O}$), 1695 ($\text{C}=\text{O}$), 1440 (C-N), 1200 (C-O), 1170 ($\text{P}=\text{O}$). m/z (FAB) 406 (MH^+ , 100), 243 ($\text{Ph}_2\text{POCH}_2\text{CHO}^+$, 60), 217 (25), 201 (PH_2PO^+ , 42). Anal. calcd. for $\text{C}_{23}\text{H}_{20}\text{NO}_4\text{P}$: C, 68.1; H, 4.9; N, 3.5; P, 7.8. Found: C, 68.1; H, 5.2; N, 3.4; P, 7.7.

(S)-(-)-N-(1-oxo-2-diphenylphosphinoyl)ethyl-4-benzyl-2-oxazolidinone (6c): (0.6 g, 1.48 mmol, 13%; acetone was used as eluent) obtained as a white solid after recrystallization from ethyl acetate: $[\alpha]_D + 50^\circ$ (cl, CHCl_3); mp 170-172°C. ^1H NMR (CDCl_3): δ 2.50 (1H, dd, $J =$

13.4, 10.2 Hz, HCHO), 3.20 (1H, dd, $J = 13.4, 3.3$ Hz, HCHO), 4.00 (1H, overlapping, dd, $J = 8.7, 7.8$ Hz, HCHPh) 4.05 (1H, dd, $J_{\text{PH}} = 14.8, J_{\text{HH}} = 13.7$ Hz, HCHPO), 4.55 (1H, overlapping ddd, CH), 7.10-7.90 (15H, m, Ar-H). ^{13}C NMR (CDCl_3): δ 37.60 (PhCH_2), 38.12 (d, $J_{\text{PC}} = 59.00$ Hz, PCH_2), 55.57 (CH), 66.01 (CH_2O), 127.17 (CH), 128.65 (d, $J_{\text{PC}} = 25.0$ Hz, CH), 129.05 (d, $J_{\text{PC}} = 7.4$ Hz, CH), 130.99 (CH), 131.00 (d, $J_{\text{PC}} = 10.0$ Hz, CH), 132.37 (CH), 136.36 (C), 153.54 (CO), 165.28 (d, $J_{\text{PC}} = 6.4$ Hz, CO). IR (KBr, ν_{max} , cm^{-1}): 1790 (C=O), 1440 (C-N), 1200 (C-O), 1170 (P=O). m/z (FAB) 420 (MH^+ , 100), 264 (17), 243 ($\text{Ph}_2\text{POCH}_2\text{CHO}^+$, 85), 215 (10), 201 (Ph_2PO^+ , 58), 165 (7), 117 (9), 91 (18). Anal. calcd. for $\text{C}_{24}\text{H}_{22}\text{NO}_4\text{PCl}$: C, 68.7; H, 5.2; N, 3.3; P, 7.4. Found: C, 68.4; H, 5.3; N, 3.3; P, 7.3.

Spectroscopic data of 2-(diphenylphosphinoyl) ethanoic acid (13a):

^1H NMR (CDCl_3): δ 3.55 (2H, d, $J_{\text{PH}} = 15.0$ Hz, CH_2PO), 7.45-7.75 (10H, m, Ar-H), 10.65 (1H, brs, OH). IR (KBr, ν_{max} , cm^{-1}): 3100 (OH str.), 1720 (C=O str.), 1250 (C-O str.), 1170 (P=O).

RESULTS AND DISCUSSION

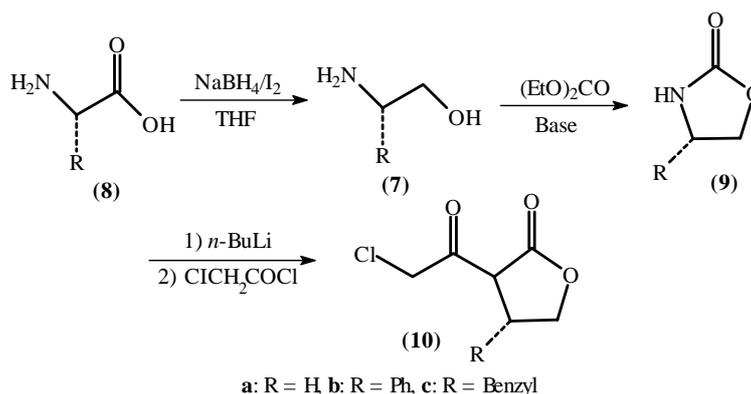
The synthesis of these novel chiral side chain phosphine oxides consists of the following steps: i) Direct reduction of α -amino-acids to β -amino alcohols, the use of α -aminoacids was to introduce an asymmetric centre into target molecule¹⁵⁻²⁰, ii) Transformation of β -amino alcohols into the corresponding chiral auxiliaries oxazolidinones, iii) N-chlorination of the oxazolidinones and iv) The application of Arbusov reaction.

The β -amino alcohols (**7a-d**) were prepared by direct reduction of the commercially available α -amino acids (**8a-d**) with NaBH_4/I_2 ¹⁶⁻¹⁸ in anhydrous THF. In all cases, the reduction was completed without any detectable racemization. These β -amino alcohols on treatment with equimolar quantity of diethyl carbonate yielded the 4-substituted oxazolidinone (**9a-c**). N-chlorination of these oxazolidinones with chloroacetyl chloride in the presence of $n\text{-BuLi}$ in anhydrous THF at -78°C gave the desired chloroamides (**10a-c**) in excellent yields which were identified spectroscopically (**Scheme-1**).

After preparation of 3-chloroacetyl-4-substituted-2-oxazolidinones, the next step was to perform the Arbusov reaction by addition of chloroamides (**10c**) solution in dry THF to the *in situ* formed methoxy diphenylphosphine (**11**) to give respectively phosphine oxides (**5c**) and (**6c**). These were readily separated by column chromatography on silica gel and their structures were fully confirmed by microanalytical results and spectral data. In contrast the Arbusov reaction, it was noted that the phosphinoyl group can be formed by using methoxy diphenylphosphine instead of what usually used in Arbusov reaction trialkoxy phosphine such as triethoxyphosphine.

Analogous reaction of chloroamides (**10b**) with methoxy diphenyl-

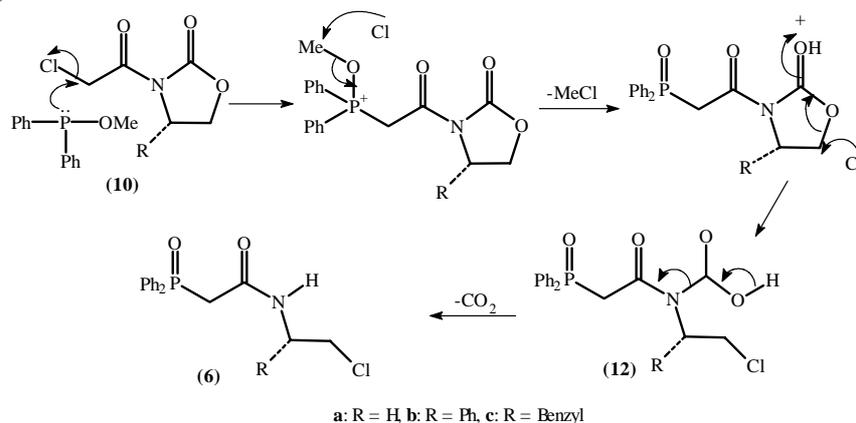
phosphine resulted in the formation of **(6b)** and its structure was also confirmed by microanalytical results and spectral data. The product **(5b)** expected to be formed was not detected since the mixture was heated for shorter time (1 h).



(Scheme-1)

To explore the versatility of these reactions, achiral chloroamide **10a** (obtained from cheap, commercially available β -amino alcohol **7a-c**) yielded phosphine oxides (**5a** and **6a**).

On the basis of the above results, a reaction sequence for the formation of **(5a-c)** and **(6a-c)** is outlined in **(Scheme-2)**. The nucleophilic attack of chlorine ion present *in situ*, since the reaction was performed in the presence of N, N'-dimethylaniline hydrochloride, at C-3 position of the oxazolidinone ring gives the intermediate **(12a-c)**, which are converted into the corresponding **(5a-c)** by heat decarbonylation.



Scheme-2

Conclusion

We have developed a simple efficient method that allows for synthesising phosphine oxides (**5a-c**) and (**6a-c**) utilising the easily prepared chloroamides (**10a-c**) followed by application of Arbusov reaction. Further more application of these phosphine oxides (**6a-c**) for producing chiral α -phosphinoyl carboxylic acids after introducing a chiral centre to α -position of compounds (**6a-c**) followed by hydrolysis could give further products such as α -alkyl- α -substituted acetic acid (**13b**) then can be reduced to further interesting β -diphenylphosphinoyl alcohols such as (**14b**) (Fig. 2) is under investigation, since we successfully hydrolysed the compounds (**6a-c**) before introducing the chiral centre and the α -diphenylphosphinoyl acetic acid (**13a**) (Fig. 3) was obtained.

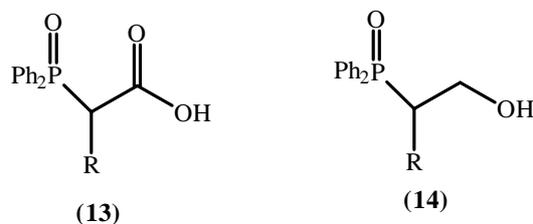


Fig. 3

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