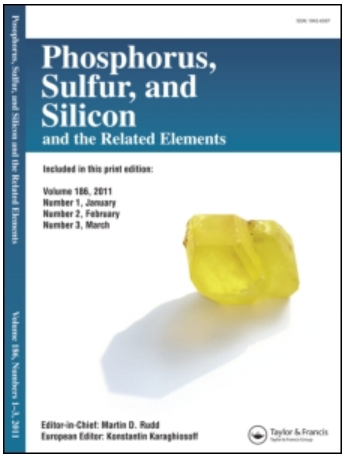

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One Pot Synthesis of Diastereomeric Phosphonates

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ONE POT SYNTHESIS OF DIASTEREOMERIC PHOSPHONATES

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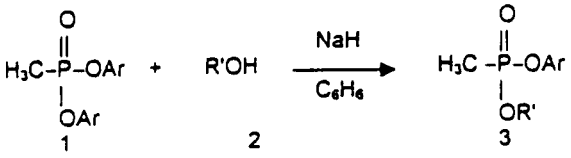
The reaction of diaryl methylphosphonate with sterically hindered alcohols in presence of sodium hydride provide arylalkyl methylphosphonate esters with high diastereoselectivity at the phosphorus center.

Keywords: Transesterification; Phosphonate esters; Diastereoselectivity; Sodium hydride

INTRODUCTION

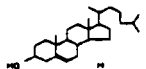
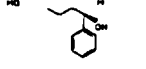
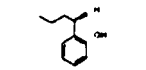
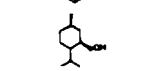
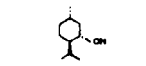
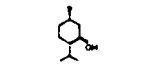
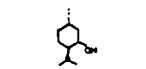
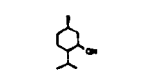
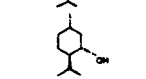
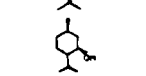
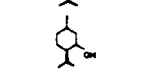
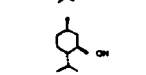
Organophosphorus compounds containing chiral isomers are of special interest because of their differential biological activities[1] and usefulness as a tool for determination of mechanism of biochemical reactions[2,3]. Apart from these properties chiral esters are also useful as transition state analogs in eliciting catalytic antibodies[4]. The reported procedure[5,6,7] for conversion of diaryl methylphosphonates by optically active alcohols demonstrated no diastereoselectivity in the resulting O-alkyl-O-aryl methylphosphonates (mixed esters). However, a recently reported method[8] which utilised n-butyl lithium has claimed the preparation of mixed esters with diastereoisomeric excess at the phosphorus center. Herein we report one pot transesterification of diaryl methylphosphonates to diastereomeric esters by optically active alcohols in the presence of sodium hydride.

* Corresponding Author.



SCHEME I

TABLE I

Entry	Compound 3 Ar OH	Compound 3 R' OH	Yield 3(%)[a]	^{31}PNMR[b]	Distribution %[c]
3a			38	27.10 (27.22[d] 26.57)	100 (97[d] 3)
3b			60	25.13 25.74	54 46
3c			58	25.67 26.28	47 53
3d			70	25.74 25.13	58 42
3e			69	25.74 (27.80[d] 25.13 27.20)	30 (42[d] 70 58)
3f			75	26.27 25.74	75 25
3g			72	26.55 25.94	10 90
3h			66	27.43 26.48	31 69
3i			62	27.36 26.41	47 53
3j			71	27.59 26.95	40 60
3k			70	27.64 27.00	30 70
3l			53	28.02 27.67	60 40

[a] Isolated yields

[b] $CDCl_3$ was used as the solvent and 85% H_3PO_4 as an external standard for ^{31}P NMR measurement

[c] The R_R:S_S ratios were determined by integration of the two product peaks in ^{31}P NMR spectra

[d] See reference 8

RESULTS AND DISCUSSION

The method consists of reaction of diaryl methylphosphonates 1 a-e with optically active alcohols 2 a-e in the presence of sodium hydride to yield O-alkyl-O-aryl methylphosphonate 3 a-l (scheme-1). The moderate to high sterically hindered alcohols 2 a-e were chosen to show the diastereoselective effeciency of the method (Table I). Monitoring of the reaction by GLC showed appearance of two new peaks at the expense of the peak due to diaryl methylphosphonate (R_t=11.88–14.49). The two new peaks were identified as phenols (R_t=1.31–2.10) and mixed esters (R_t=14.29–15.88) by comparison with R_t values of the authentic samples of corresponding phenols and esters. The generation of phenol may be explained by the direct interaction between diaryl methylphosphonate and sodium hydride under the reaction conditions employed. Although it became evident that the reaction proceeds via alkoxide anions, the direct addition of sodium hydride (in parts) in a one pot reaction proved to be advantageous because of relatively better isolated yield and convenient work-up procedure (see experimental sect. 2). The diastereoselectivity was found to be governed mostly by steric bulk at the chiral carbon atom. However, our results demonstrated that the leaving group had little or no role towards increasing the diastereomeric excess at the phosphorus center (Table I). The moderately hindered alcohols 2 b,c reacted with 1a and gave mixed esters 3b,c with poor diastereoselectivity (54:46 & 47:53 respectively). The reaction between 2d,e and 1a-e gave 3 d-l in good yield (70%-75%) with moderate to high diastereoselectivity (Table I). Interestingly, when (+)cholestrol 2a was reacted with 1a in presence of sodium hydride, the product was 3 a, as a single diastereoisomer (Table I).

In conclusion, our results indicate that this method is a valuable addition to the synthesis of mixed esters and that diastereoselectivity is mainly due to steric hindrance at the chiral carbon atom of the alcohols.

EXPERIMENTAL

Boiling points reported are uncorrected. IR Spectra were recorded on a Nicolet FT-IR Impact 410 spectrophotometer. The ^1H and ^{31}P NMR spectra were recorded on Jeol Ex-90 as well as a Bruker Avance DPX-400 in

$CDCl_3$ with $(CH_3)_4Si$ as internal standard and 85% H_3PO_4 as external standard, respectively. Mass spectra were obtained from Finnigan Mat TSQ 7000, at EI (70ev). Monitoring of reactions was done on a Netel GC Micro-9100 equipped with a FID detector, carrier gas nitrogen, (flow rate 30 ml/min) and packed Column – SE-30, using temperature programming as: initial oven temperature 100°C, iso time 2 min, ramp rate 10°C/min, maximum temperature 280°C, iso time 2 min. Injector and FID detector temperatures were 300°C. Silica gel (S. Merck) was used for column chromatography. Optically active alcohols and phenols procured either from Lancaster, Fluka or Aldrich chemical Co. Ltd were used. Solvents were distilled and dried before use.

Section-1

Preparation of O,O-diphenyl methylphosphonate(1a); General Procedure

A solution of phenol (2.35 g, 0.025 mol) and triethylamine (2.53 g, 0.025 mol) in dry dichloromethane (60 ml) at 0°C was added dropwise to a solution of methylphosphonic dichloride (2.66 g, 0.01 mol) in dichloromethane (50 ml) and then the mixture was stirred at room temperature for 1 hr. The precipitated salt was filtered, and the filtrate after washing with saturated sodium chloride solution (2 x 10 ml) was dried with anhydrous $MgSO_4$. The removal of solvent followed by distillation of the residue at 148°C/0.3 mmHg (lit[9]. 190–195°C /11mmHg) afforded an oily liquid 4 gm (80%), R_t=11.88; IR(KBr) : 3069(Ar-H),1262(P=O),1191(P-O-Ar), 934 (cm^{-1}); ^1H NMR(90MHz,$CDCl_3$)δ : 1.75 (3H,d,J_{HP}=17.9 Hz), 7.0–7.4 (10H,m); ^{31}P NMR : 24.55(lit[10]. 24.52 ppm); M.S : m/z 248 (M^+), 170, 155, 94, 77.

Compounds 1b-e were prepared by a similar procedure and the spectral and analytical data are given as follows:

O,O-di-4-chlorophenyl methylphosphonate (1b)

Oily liquid; Yield 77%; b.p 160°C/0.1mmHg (lit[9] 245°C/20mmHg); R_t=15.09; IR (KBr) : 3096 (Ar-H),1266 (P=O), 1198(P-O-Ar),928(cm^{-1}); ^1H NMR(90MHz,$CDCl_3$)δ : 1.78 (3H,d,J_{HP}=17.9 Hz), 6.97–7.35 (8H,m); ^{31}P NMR : 24.6 ppm (lit[10]24.8ppm); M.S : m/z 316 (M^+),238,189,127, 111,99, 75,73.

O,O-di-2-chlorophenyl methylphosphonate (1c)

Oily liquid; Yield 65%; b.p 176°C/0.1mmHg; R_t=14.49; IR(KBr) : 3096(Ar-H),1261(P=O),1061(P-O-Ar),934(cm^{-1}); ^1H NMR (90MHz, $CDCl_3$)δ : 1.92(3H,d,J_{HP}=17.9 Hz), 7.05–7.40 (8H,m); ^{31}P NMR : 25.8ppm; M.S : m/z 316 (M^+),189,127,111,99,75,73.

O,O-di-4-methylphenyl methylphosphonate (1d)

Oily liquid; Yield 70%; b.p 152°C/0.1mmHg(lit[9]220–225°C/12mmHg); R_t=14.09; IR(KBr) : 3033,(Ar-H),1268(P=O), 1194(P-O-Ar),943(cm^{-1}); ^1H NMR(400MHz,$CDCl_3$)δ : 1.75(3H,d,J_{HP}=17.9 Hz),2.30(3H,s), 7.05 (8H,m); ^{31}P NMR : 24.7 ppm; M.S : m/z 276 (M^+),197,169,91,77.

O,O-di –4-nitrophenyl methylphosphonate (1e)

White crystals; Yield 52%; m.p 119°C (lit[11]119–120°C); IR(KBr) : 3112(Ar-H),1589,1515,1347,1265 (P=O),1206 (P-O-Ar), 935 (cm^{-1}); ^1H NMR(400MHz,$CDCl_3$)δ : 1.98 (3H,d,J_{HP}=17.9 Hz), 7.4,8.3 (8H,m); ^{31}P NMR: 25.7ppm.

Section-2

Preparation of diastereomers of O-menthyl-O-phenyl methylphosphonate(3d); General procedure

Sodium hydride (0.3 g, 0.0125 mol) was added to a refluxing mixture of O,O- diphenyl methylphosphonate (2.48 g, 0.01 mol) and R(+) menthol (2 g, 0.0125 mol) in dry benzene (40 ml). After 10 hrs reflux, the resultant mixture was filtered and the benzene layer was separated. The residual material was treated with hexane (70 ml) and the insoluble portion was rejected. The hexane layer was then washed with 2N NaOH (2 ml x 2) followed by washing with distilled water (10 ml × 2). The organic layer so obtained was dried over anhydrous $MgSO_4$and removed by distillation at atmospheric pressure The resulting liquid was subjected to column chromatography on silica gel, the eluting solvent was a mixture of benzene: hexane (90:10). An appropriate fraction was collected and solvent stripped off. R_t=14.36.

IR(KBr) : 2954,2926,1256(P=O),1209(P-O-Ar),1014(P-O-R'),920 (cm^{-1}); ^1H NMR(90MHz, $CDCl_3$) δ : 0.70(3H,d,J_{HH}=7.1 Hz), 0.90 (6H,d,J_{HH}=7.1 Hz), 1.65,1.62 (3H,d,J_{HP}=17.9 Hz), 4.20(1H,m), 7.14–7.45(5H,m); M.S :

m/z 310(M^+),173,155,138,123,95,77; Anal. Calcd : C,65.8; H,8.7; Found : C,66.2; H,8.7.

Compounds 3a-c,3e-l were prepared according to the method as described above. The spectral and analytical data are given as follows:

O-cholestryl-O-phenyl methylphosphonate 3a

Eluting solvent : Benzene : Acetone (80:20); IR(KBr) : 2961,2925,1260 (P=O),1093,1020(P-O-R'),795(cm^{-1}); ^1H NMR(400MHz,$CDCl_3$)δ : 0.69–2.36(Cholestryl proton), 1.3(3H,d,J_{HP}=17 Hz), 5.46[1H,m (C=CH)], 7.5–7.7(5H,m).

O-1-phenylbutyl-O-phenyl methylphosphonate 3b

Eluting solvent : Hexane : acetone (97:3); R_t=13.94; IR(KBr) : 2955,2926,1257(P=O)1209(P-O-Ar),1015(P-O-R'),926 (cm^{-1}); ^1H NMR (90MHz,$CDCl_3$)δ : 0.88(3H,t,J_{HH}=7.1 Hz), 1.25(4H,s), 1.56(3H,d, J_{HP}=17.9 Hz), 7.2–7.32(5H,m); M.S : m/z 304(M^+), 261,183,173,156, 133,117, 91,78; Anal. Calcd : C, 67.1; H,6.9; Found : C,67.4; H,7.3.

O-1-phenylbutyl-O-phenyl methylphosphonate 3c

Eluting solvent : Hexane : acetone (97:3); R_t=13.99; IR (KBr) : 2960,2929,1259 (P=O),1208 (P-O-Ar),1020 (P-O-R'),938, 799(cm^{-1}); ^1H NMR (90MHz,$CDCl_3$)δ : 0.88 (3H,t,J_{HH}=7.1 Hz),1.25 (4H,s),1.56 (3H,d, J_{HP}=17.9 Hz),7.2–7.32(5H,m); M.S : m/z 304(M^+),261,173,155,132, 117,91,77; Anal. Calcd : C,67.1; H,6.9; Found : C,67.6; H,7.3.

O-menthyl-O-phenyl methylphosphonate 3e

Eluting solvent : Benzene : Hexane (90:10) R_t=14.29; IR(KBr) : 2955,2926,1256 (P=O),1210 (P-O-Ar),1015(P-O-R'),926(cm^{-1}); ^1H NMR(90MHz,$CDCl_3$)δ : 0.63 (3H,d,J_{HH}=7.1 Hz), 0.83 (6H,d,J_{HH}=7.1 Hz), 1.58,1.55 (3H,d,J_{HP}=17.9 Hz),4.30(1H,m),7.1–7.38 (5H,m); M.S : m/z 310(M^+),173,155,138,123, 95,77; Anal. Calcd : C,65.8; H,8.7; Found : 66.2; H,8.7.

O-menthyl-O-4-chlorophenyl methylphosphonate 3f

Eluting solvent : Benzene : Hexane (90:10); R_t=15.88; IR (KBr) : 2955,2927,1255 (P=O),1216 (P-O-Ar),1014 (P-O-R'), 923(cm^{-1}); ^1H NMR(90MHz,$CDCl_3$)δ : 0.64(3H,d,J_{HH}=7.1 Hz), 0.88(6H,d,J_{HH}=7.1

Hz),1.60, 1.58(3H,d,J_{HP}=17.9 Hz), 4.1(1H,m),7.05–7.35(4H,m); M.S : m/z 344(M^+),207,189,138,128,95; Anal. Calcd : C,59.3; H,7.8; Found : 59.6; H,8.0.

O-menthyl-O-4-chlorophenyl methylphosphonate 3 g

Eluting solvent : Benzene : Hexane:Acetone (93:5:2); R_t=15.85; IR(KBr) : 2957,2925,1260 (P=O),1216 (P-O-Ar), 1093(P-O-R'),925 (cm^{-1}); ^1H NMR(90MHz,$CDCl_3$)δ : 0.7(3H,d,J_{HH}=7.1 Hz), 0.92 (6H,d,J_{HH}= 7.1 Hz),1.63,1.60(3H,d,J_{HP}=17.9 Hz), 4.20 (1H,m),6.5–7.05 (4H,m); M.S : m/z 344 (M^+), 207,189,138,128,123,95; Anal. Calcd : C,59.3; H,7.8; Found : C,59.6; H,8.0.

O-menthyl-O-2-chlorophenyl methylphosphonate 3h

Eluting solvent : Benzene; R_t = 15.64; IR(KBr) : 2955,2926,1266 (P=O),1223 (P-O-Ar),1015 (P-O-R'),950(cm^{-1}); ^1H NMR (90MHz, $CDCl_3$)δ : 0.67 (3H,d,J_{HH}=7.1 Hz),0.89 (6H,d,J_{HH}=7.1 Hz),1.68 (3H,d,J_{HP}= 17.9 Hz), 4.17(1H,m),7.50–7.73(4H,m); M.S : m/z344 (M^+),309,207,189,171,138,128, 123,95; Anal. Calcd : C,59.3; H, 7.8; Found : C,59.8; H,8.2.

O-menthyl-O-2-chlorophenyl methylphosphonate 3i

Eluting slovent : Benzene; R_t =15.17; IR(KBr) : 2961,2926,1261(P=O), 1223(P-O-Ar),1019(P-O-R'),927(cm^{-1}); ^1H NMR (90MHz,$CDCl_3$)δ : 0.65 (3H,d,J_{HH}=7.1 Hz),0.84 (6H,d,J_{HH}=7.1 Hz),1.68 (3H,d,J_{HP}= 17.9 Hz),4.22 (1H,m), 7.52–7.72 (4H,m); M.S : m/z 344(M^+),309,207,189, 171,138,128, 123,95; Anal. Calcd : C,59.3; H,7.8; Found : C,60.1; H,8.1.

O-4-menthyl-O-4-methylphenyl methylphosphonate 3j

Eluting solvent : Hexane : Ethyl acetate (75:25); R_t=15.25; IR(KBr) : 2955,2926,1257(P=O),1215 (P-O-Ar),1014 (P-O-R'),923(cm^{-1}); ^1H NMR (400MHz,CDCl3)δ : 0.77 (3H,d,J_{HH}=8 Hz), 0.85 (6H,d,J_{HH}=8 Hz), 1.57,1.60,(3H,d,J_{HP}=17.2 Hz),2.31(1H,s), 4.2(1H,m), 7.50–7.73(4H,m); M.S : m/z 324 (M^+),187,169,138,123,108,91; Anal. Calcd : C,66.6; H,8.9; Found : C,66.8; H,9.0.

O-menthyl-O-4-methylphenyl methylphosphonate 3k

Eluting solvent : Hexane : Ethyl acetate (75:25); R_f=14.81; IR(KBr) : 2955,2869,1257(P=O),1216 (P-O-Ar),1014(P-O-R'), 923(cm^{-1}); ^1H NMR (400MHz,CDCl3)δ : 0.67 (3H,d,J_{HH}=8 Hz), 0.84 (6H,d,J_{HH}=8 Hz), 1.57,1.60 (3H,d,J_{HP}=17.2 Hz), 2.31(3H,s),4.25(1H,m),7.01(4H,m); M.S : m/z 324(M^+), 187,169,138,123,108,91; Anal. Calcd : C,66.6; H,8.9; Found : C,66.8; H.9,0.

O-menthyl-O-4-nitrophenyl methylphosphonate 3l

IR (KBr) : 2961,2625,1260 (P=O), 1097,1019(P-O-R')(cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$)δ : 0.58 (3H,d,J_{HH}=8Hz),0.74 (6H,d,J_{HH}= 8Hz),1.64 (3H,d,J_{HP}=16 Hz),6.8–8.18(4H,m).

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