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A CONVENIENT SYNTHESIS OF CYCLOALKYLPHOSPHONATES FROM (PHENYLSULFONYL)METHYLPHOSPHONATE

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Abstract : Cycloalkylphosphonate derivatives were synthesized in excellent overall yields, in two steps by the bis-alkylation of (phenylsulfonyl)methylphosphonate with ω-dibromoalkanes in the presence of a phase transfer catalyst followed by desulfonation.

Phosphonate derivatives are of importance in organic chemistry because of their use as intermediates for the preparation of alkene derivatives by the Horner-Wadsworth-Emmons condensation[1] and in the fields of pharmaceuticals and agrochemicals owing to their biological activities.[2] Although a number of synthetic methods of unsubstituted cycloalkylphosphonates have been developed

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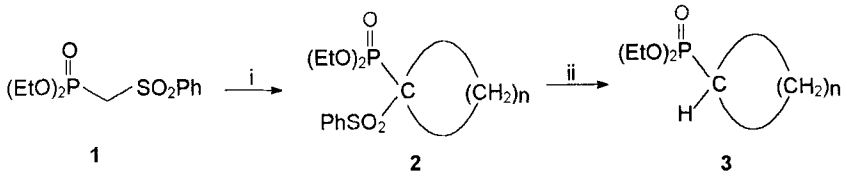
with the goal of providing a route this class of compounds, they have limitations in terms of the conditions employed and yields.

Cycloalkylphosphonates have been prepared, in moderate yields, by the peroxide initiated free radical reaction of dialkyl phosphites with cycloalkenes.[3] The alcoholysis of chloroaluminate complexes which are obtained from the reaction of phosphorus trichloride with cycloalkyl chlorides in the presence of aluminum trichloride, leads to cycloalkylphosphonates in moderate yield.[4] They are also obtained by desulfonation of (1-alkylthio)cycloalkylphosphonates, which result from the reaction of cycloalkane dithiols with trialkyl phosphites.[5] Recently, cycloalkylphosphonates were obtained by the alkylation of trichloromethyl-phosphonates with ω-dibromoalkanes, via the corresponding α-trimethylsilyl cycloalkylphosphonates[6] or electrochemical alkylation of trichloromethyl-phosphonate in the presence of ω-dibromoalkanes.[7]

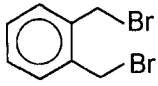
Herein, we report a two step synthesis of cycloalkylphosphonates **(3)** starting from (phenylsulfonyl)methylphosphonate **(1)**, which is easily available.[8] It was performed by the bis-alkylation of (phenylsulfonyl)methylphosphonate **(1)** with ω-dibromoalkanes in the presence of base followed by desulfonation.[9] The (phenylsulfonyl)methylphosphonate **(1)** was treated with aqueous NaOH and ω-dibromoalkane in the presence of dodecyltrimethylammonium chloride as a phase transfer catalyst. Reaction mixture was stirred for 20 h at room temperature, affording (phenylsulfonyl)cycloalkylphosphonate **(2)** in excellent yields. The



1 2 3

Scheme 1 i, aq. NaOH, Br-$(CH_2)_n$-Br, dodecyltrimethylammonium chloride, rt, 20 h.
ii, Mg, cat. $HgCl_2$, EtOH/THF(3/1), rt, 12 h.

Table 1. Synthesis of 1-(Phenylsulfonyl)cycloalkylphosphonates (**2**) and Cycloalklyphosphonates (**3**)

Dihaloalkane	% Yield[a] of **2**	%Yield[b] of **3**
Br-$(CH_2)_5$-Br	98	94
Cl-$(CH_2)_4$-Cl	88	95
Br-$(CH_2)_3$-Br	88	96
cis-$ClCH_2CH{=}CHCH_2Cl$	88	97
	98	96
Br(Me)CH-$(CH_2)_3$-Br	95	95

[a] Isolated yields are based on (phenylsulfonyl)methylphosphonate (**1**).

[b] Isolated yields are based on (phenylsulfonyl)cycloalkylphosphonates (**2**).

cyclized adducts **2** were efficiently desulfonylated using magnesium in the presence of $HgCl_2$ in EtOH/THF (3:1) at room temperature over 12 h. Partitioning of the residue between water-ethyl acetate afforded the corresponding cycloalkylphosphonates **(3)** in excellent yields. The operational simplicity and overall efficiency of the two-step procedure make it competitive with other approaches using alkylation of trichloromethylphosphonate. The present synthetic route is recommended as a practical preparation of cycloalkylphosphoantes (**3**).

Experimental Section

^1H and ^{13}C NMR were measured at 200 and 50 MHz respectively, in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on HP 5985A or Jeol HX100/HX110. Column chromatography was performed on Merck silica gel 60 (230-400 mesh).

Synthesis of 1-(Phenylsulfonyl)cycloalkylphosphonates (2) - A suspension of dodecyltrimethylammonium chloride (0.61g, 20 mmol) in 50% aqueous NaOH (6mL) was treated with a solution of diethyl (phenyl sulfonyl)methylphosphonate (**1**, 2.0 mmol) in ω-dibromoalkane(4mL), The reaction mixture was stirred vigorously at room temperrature for 20 h and then poured into methylene chloride(20mL) and water added until all solid had dissolved. The organic layer

was washed with water and brine, dried over $MgSO_4$, and concentrated. The residual oil was purified by silica gel column chromatography.

Diethyl 1-(phenylsulfonyl)cyclobutylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.21(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 2.21-3.1(m, 6H, H-ring), 4.08(m, 4H, $CH_3\underline{CH_2}O$), 7.49-7.68(m, 3H, Ph), 7.95-8.07(m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.27(d, *J*=5.7), 25.95(d, *J* 4.35), 63.20(d, *J*=6.6), 128.4, 130.2, 133.7; MS(*m/z*) 332(M^+,1.1), 191(28), 163(21), 135(100).

Diethyl 1-(phenylsulfonyl)cyclophentylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.22(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 1.65-2.70(m, 8H, H-ring), 4.11(m, 4H, $CH_3\underline{CH_2}O$), 7.48-7.65(m, 3H, Ph), .01-8.08(m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.23(d, *J*=6), 26.74(d, *J*=4), 32.17, 63.16(d, *J*=6.9), 128.29, 130.87, 133.70; MS(*m/z*) 346(M^+,0.8), 205(48), 149(42), 67(100).

Diethyl 1-(phenylsulfonyl)cyclohexylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.67(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 1.20-2.30(m, 10H, H-ring), 4.08(m, 4H, $CH_3\underline{CH_2}O$), 7.40-7.65(m, 3H, Ph), 7.92-8.10(m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.23(d, *J*=5.9), 21.30(d, *J*=3.1), 24.25, 26.95, 62.98(d, *J*=6.9), 128.12, 131.03, 133.53; MS(*m/z*) 360(M^+,2.0), 219(38), 163(25), 81(100).

Diethyl 1-(phenylsulfonyl)-3-cyclopentenylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.27(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 3.01-3.68(m, 4H, H-ring), 4.17(m, 4H, $CH_3\underline{CH_2}O$), 5.54(s, 2H, -CH=CH-), 7.42-7.68(m, 3H, Ph), 7.95-8.03(m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.24(d, *J*=6), 38.89, 62.98(d, *J*=6.9),

127.57, 128.38, 130.71, 133.85; MS(*m/z*) 344(M^+,2.1), 203(78), 175(21), 147(100).

Diethyl 1-(phenylsulfonyl)-2,3-dihydro-1H-inden-2-ylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.22(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$) , 3.6-3.95(m, 4H, H-ring), 4.17(m, 4H, $CH_3\underline{CH_2}O$), 7.06(s, 4H, Ph), 7.3-7.65(m, 3H, Ph), 7.9-8.0(m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.20(d, *J*=6), 38.41, 63.63(d, *J*=6.8), 123.81, 127.02, 128.32, 130.50, 133.85; MS(*m/z*) 394(M^+,11.2), 253(69), 197(52), 115(100).

Diethyl 1-(phenylsulfonyl)-2-methylcyclopentylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.29(m, 9H, $\underline{CH_3}CH_2O$,-CH(CH_3)-CH_2-), 1.4-3.85(m, 7H, H-ring), 4.06(m, 4H, $CH_3\underline{CH_2}O$), 7.4-7.7(m, 3H, Ph), 8.0-8.2(m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.12(d, *J*=6.2), 16.23(d, *J*=5.9), 26.49(d, *J*=5.1), 33.03, 63.21(d, *J*=7), 128.31, 130.88, 134.01; MS(*m/z*) 360(M^+,7.0), 219(28), 163(12), 81(100).

Synthesis of cycloalkylphosphonates (3)- A mixture of 1-(phenylsulfonyl) cycloalkylphosphonates (1.0 mmol), Mg (0.12g, 5 mmol, powder, -50mesh), and a catalytic amount of $HgCl_2$ in EtOH-THF(3/1, 10mL)was stirred for 12 h at room temperature. The reaction mixture was poured into cold 0.5N HCl solution and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried anhydrous $MgSO_4$, filtered, and concentrated.

The residual oil was purified by flash column chromatography using ethyl acetate/ hexane (1/1) as an eluent.

Diethyl cyclobutylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.31(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 1.96-2.51(m, 6H, H-ring), 2.70(m, 1H, HC-P), 4.05(m, 4H, $CH_3\underline{CH_2}O$); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.58, 20.17(d, *J*=18), 22.53(d, *J*=6.2), 29.66, 61.55; MS(*m/z*) 192(M^+,2.0), 167(23), 149(89), 43(100); HRMS: calcd for $C_8H_{17}O_3P$ 192.0915, found 192.0909.

Diethyl cyclopentylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.31(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 1.45-2.18(m, 9H, H-ring), 4.10(m, 4H, $CH_3\underline{CH_2}O$); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.51(d, *J*=5.75), 26.30(d, *J*=11.9), 27.04, 29.66, 35.08(d, *J*=145.85), 61.43(d, *J*=6.6); MS(*m/z*) 206(M^+,0.9), 167(18), 149(45); HRMS: calcd for $C_9H_{19}O_3P$ 205.0994, found 205.0981.

Diethyl cyclohexylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.29(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 1.4-2.1(m, 11H, H-ring), 4.05(m, 4H, $CH_3\underline{CH_2}O$); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.49(d, *J*=5.7), 25.83(d, *J*=4.6), 26.26, 29.66, 35.68(d, *J*=141.7), 61.38(d, *J*=6.8); MS(*m/z*) 220(M^+,0.8), 221(20), 149(25), 81(64); HRMS: calcd for $C_{10}H_{21}O_3P$ 220.1228, found 220.1267.

Diethyl 3-cyclopentenylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.32(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 2.41-2.70(m, 5H, H-ring), 4.12(m, 4H, $CH_3\underline{CH_2}O$), 5.69(s, 2H, -CH=CH-);^{13}C NMR ($CDCl_3$, 50MHz) δ 16.52(d, *J*=5.8), 29.68, 31.19, 33.77, 61.72 129.27(d, *J*=10.55); MS(*m/z*) 204(M^+,1.0), 149(78), 71(25),

57(70); HRMS: calcd for $C_9H_{17}O_3P$ 204.0915, found 204.0910.

Diethyl 2,3-dihydro-1H-inden-2-ylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.31(t, *J*=7 Hz, 6H, $\underline{CH_3}CH_2O$), 2.7-3.4(m, 5H, H-ring), 4.12(m, 4H, $CH_3\underline{CH_2}O$), 7.11-7.3(m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.5(d, *J*=5.8), 29.68, 33.82, 36.60, 61.75(d, *J*=6.70), 124.28, 126.59; MS(*m/z*) 254(M^+, 1.4), 116(68), 83(28), 57(83); HRMS: calcd for $C_{13}H_{19}O_3P$ 254.1071, found 254.1054.

Diethyl 2-methylcyclopentylphosphonate ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.11(t, *J*=7 Hz, 3H, -CH(CH_3)-CH_2-), 1.32(t, *J*=7, 6H, $\underline{CH_3}CH_2O$), 1.4-2.4(m, 8H, H-ring), 4.10(m, 4H, $CH_3\underline{CH_2}O$); ^{13}C NMR ($CDCl_3$, 50MHz) δ 16.13(d, *J*=5.6), 16.30(d, *J*=6.1), 26.42(d, *J*=5.4) 28.01, 29.31, 35.19, 63.34(d, *J*=6.7); MS(*m z*) 220(M^+,1.6), 149(48), 111(24), 83(29); HRMS: calcd for $C_{10}H_{21}O_3P$ 220.1228, found 220.1212.

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