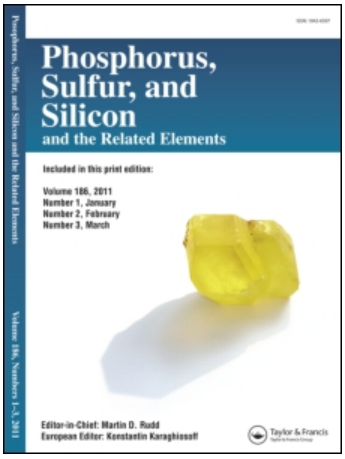

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α-FUNCTIONAL CYCLOALKYLPHOSPHONATES I. SYNTHESIS

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α-FUNCTIONAL CYCLOALKYLPHOSPHONATES I. SYNTHESIS

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Cycloalkylphosphonates **2** of different sizes (from cyclopropyl to cycloheptyl) bearing various functional groups Z in α position were synthesized by bis-alkylation of α-functional methylphosphonates **1** and ω-dibromoalkanes in presence of base. The choice of the basic system is determined by the nature of Z. With powerful electron-withdrawing groups, NaH-THF/DMSO (Method A, for Z = CN, SO_2R) or liquid-solid phase transfer process [Method B, for Z = COOR, $P(O)(OEt)_2$] proved to be the more suitable systems. For Z = aryl or SR, lithium diisopropylamide is required to achieve the deprotonation. A wide range of new phosphonates were obtained in high yields on preparative scale.

Key words: Phosphonates; cycloalkylation; carbanions; ω-dibromoalcanes; phase-transfer-catalysis.

INTRODUCTION

As compared to the α-functional phosphonates **1** popularized by the Wittig-Horner reaction, cycloalkylphosphonates **2** carrying a geminal function are much less often described. However, several compounds in this group have showed biological properties, as e.g. the herbicide "Trakephon" **3**,[1] the antileukaemic aminophosphonic acid **4** ($n = 4$),[2] the phosphonic analog **4** ($n = 2$)[3] of the phytohormone "ACC" **5** and others with potential microbiocidal activity[4] (Figure 1). As part of a program aimed at developing new functionalized phosphonates for biological screening, we have studied an efficient methodology to cycloalkylphosphonates **2**.[5]

The already described synthetical ways to **2** may be divided into two groups.

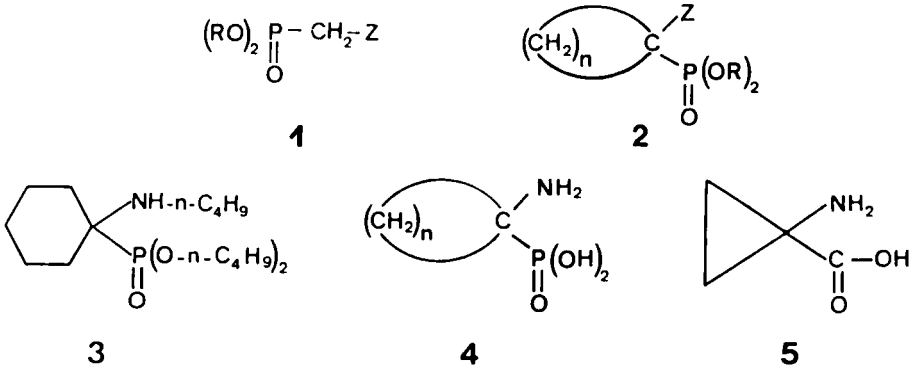
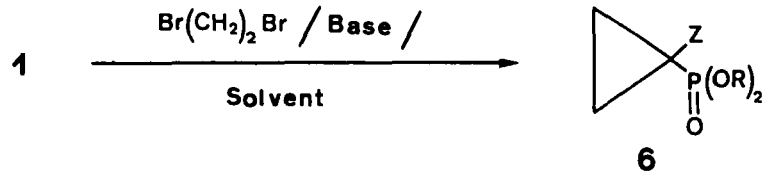


FIGURE 1



Scheme 1

- In the first one, the P—C bond is created from a pre-existent cyclic structure by Arbuzov,[6-8] Abramov[9-15] or Mannich[16-18] like-type reactions.
- In the second group of methods, the cycle is built on a suitable phosphonate. These methods lead only to the cyclopropylphosphonates by 1,3-dipolar cycloaddition between a diazocompound and an alkene, followed by decomposition of the pyrazoline intermediate,[19-27] or by direct carbanionic cyclopropanation on reacting a dimethylsulfonium methylide[28] or an α-nitrocarbanion[29] with an α-functionalized alkenylphosphonate.

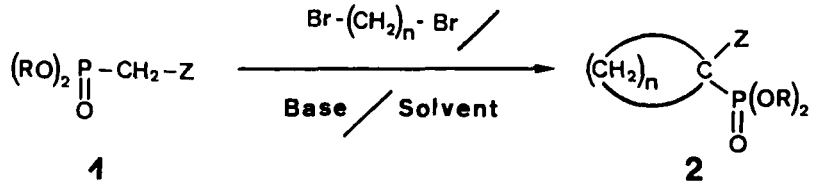
Another carbanionic route to α-functional cyclopropylphosphonates **6** lies in the bis-alkylation of phosphonates **1** with 1,2-dibromoethane as shown in Scheme 1. The choice of base and solvent depends on the nature of Z. When Z is an imino group, the deprotonation requires the powerful LDA-THF system, while an isonitrile group in α position allows cyclopropanation by the NaH-DMSO-diethylether system.[3] Finally, when Z = CN, the ion-pair extraction technique ($NaOH-H_2O$/TEBAC) provides an economical route to **6** (Z = CN, R = C_2H_5); however these last conditions are ineffective for Z = $COOC_2H_5$.[30]

To our knowledge such a methodology has been rarely used for the synthesis of others cycloalkylphosphonates **2** ($n > 2$),[31, 32] whereas cyclisation, under basic conditions, of ω-halogenoalkylmalonic esters is a familiar and important method for the synthesis of gem-difunctional cyclic compounds.[33]

Owing to the accessible phosphonates **1** and the easy process for their preparation, we decided to extend Scheme 1 to several cycles and functional groups (Scheme 2).

RESULTS AND DISCUSSION

The above Scheme 2 was tested on about twenty phosphonates **1** covering a broad range of functions Z, which may be divided into two classes:



Scheme 2

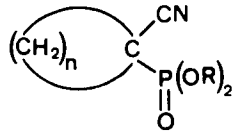
- In class I, we listed powerful electron-withdrawing groups as CN, $C_6H_5SO_2$, CH_3SO_2, $COOC_2H_5$, $P(O)(OC_2H_5)_2$.
- Class II contains groups showing weaker electron-withdrawing character as aryls, C_6H_5S, CH_3S.

All these phosphonates were either commercially available or prepared by conventional methods. In most cases R = C_2H_5, more rarely *i*-C_3H_7 or *n*-C_4H_9. Finally, commercial ω-dibromoalkanes vary from $n = 2$ to $n = 6$. For our purposes, we selected the following three methods of cyclisation:

- In method A, we used a base/solvent system analog to the one described early for the isonitrile series[34,3]: NaH/THF-DMSO (80 vol–20 vol), at room temperature.
- As method B we utilized the K_2CO_3/acetonitrile system, at 60°C, through the solid-liquid phase-transfer-catalysis (PTC) process.[35] The moderate basicity of systems developed in methods A and B was suitable for phosphonates of class I only.
- For the ones of class II, we selected the more potent basic system: LDA in THF at −60°C (method C).

First, we evaluated comparatively methods A and B for the nitrile series (Table 1). Progress of the reactions was monitored by gas chromatography (GC) and crude products were purified by distillation or liquid chromatography over silica. In method A, reagents were employed in stoichiometric proportions; in method B,

TABLE 1
α-Cyanoalkylphosphonates



Entry	*n*	R	Yield % dist. Meth. A	Yield % dist. Meth. B	^{31}P-NMR ($CDCl_3$) δ ppm	BP°C/mmHg
1-a	2	C_2H_5	85	90	16.20	100/0.5
1-b	2	*n*-C_4H_9	80	90	19.96	116/0.45
1-c	2	*i*-C_3H_7	70	73	13.76	78/0.5
1-d	3	C_2H_5	70	79	17.56	100/0.2
1-e	3	*n*-C_4H_9	—	80	21.22	120/0.45
1-f	3	*i*-C_3H_7	—	73	15.37	94/0.5
1-g	4	C_2H_5	70	85	20.04	104/0.2
1-h	4	*n*-C_4H_9	—	89	23.71	134/0.3
1-i	4	*i*-C_3H_7	—	75	17.78	108/0.4
1-j	5	C_2H_5	61	80	18.39	114/0.2
1-k	5	*n*-C_4H_9	—	89	21.97	142/0.3
1-l	5	*i*-C_3H_7	—	72	16.28	114/0.4
1-m	6	C_2H_5	*	70	15.37	160/0.2

* incomplete reaction.
— not experimented.

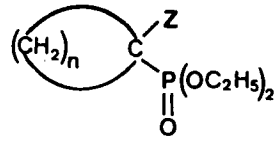
an excess of ω-dibromoalkane (2,2 eq.) proved to be indispensable for the completion of the reaction. For long chain dibromoalkanes ($n > 5$), the excess must be eliminated by steam distillation.

In each attempt of this series (except for $n = 6$, with method A), GC analysis showed total consumption of phosphonate **1**. However, method B leads to cleaner crude products and therefore higher yields after distillation; moreover the procedure of method B is easy and economical. For the two methods, the effect of R may be seen from the cyclopropane series: a slight disadvantage is observed for the isopropyl group, as confirmed for $n > 2$, in method B.

Results relating to other electron-withdrawing groups Z appear in Table 2. The powerful withdrawing sulfonyl group provided results similar to the ones of the nitrile series, including a slight superiority for method B. However, sulfonylphosphonates showed some sensitivity to distillation. With ethoxycarbonyl and diethoxyphosphonyl groups, method B proved to be inadequate: reaction was never complete and led to a mixture of products that we were not able to separate. On the other hand, method A appears obviously suitable for $n = 4$ and 5 with these two groups. Unfortunately, for $n = 2$, it was impossible again to obtain complete cyclisation; when Z = $COOC_2H_5$, progress of the reaction reached 75% (deter-

TABLE 2

Cycloalkylphosphonates bearing an α-sulfonyl, an α-ester or an α-phosphoryl group

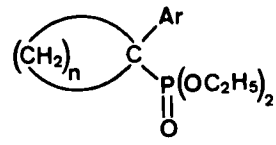


Entry	Z	n	Yield % dist. Meth. A	Yield % dist. Meth. B	^{31}P-NMR ($CDCl_3$) δ ppm	BP°C/mmHg
2-a	C_6H_5-SO_2	2	70	82	14.85	145/0.5
2-b		3	55	55	15.00	120/0.3
2-c		4	65	77	19.14	145/0.5
2-d		5	61	66	17.63	120/0.2
2-e	CH_3-SO_2	2	75	75	14.55	120/0.5
2-f		3	65	70	16.28	110/0.2
2-g		4	68	73	19.44	134/0.2
2-h		5	65	71	19.82	150/0.2
2-i	$C(O)OC_2H_5$	2	*	*	20.80	—
2-j		3	60	*	22.75	99/0.2
2-k		4	78	*	24.78	98/0.15
2-l		5	75	*	22.75	110/0.2
2-m	P(O) $(OC_2H_5)_2$	2	*	*	21.85	—
2-n		3	*	*	—	—
2-o		4	77	*	25.99	110/0.4
2-p		5	68	*	24.63	130/0.2

* incomplete reaction.
— not determined.

TABLE 3

α-Arylcycloalkylphosphonates

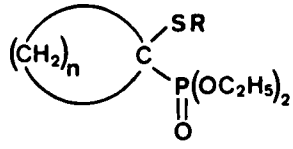


Entry	Ar	n	Yield %*	^{31}P-NMR ($CDCl_3$) δ ppm	BP°C/mmHg (or MP°C)
3-a		2	61	25.30	108/0.4
3-b	C_6H_5	3	50	26.51	100/0.2
3-c		4	56	29.30	115/0.15
3-d		5	50	27.42	120/0.4
3-e		3	45	24.78	110/0.2
3-f	2-Cl-C_6H_4	4	55	28.40	84
3-g		5	48	26.06	124
3-h	4-Cl-C_6H_4	4	58	28.55	158/0.5
3-i		5	47	26.66	154/0.1
3-j	3-CH_3-C_6H_4	4	75	29.15	140/0.5
3-k		5	50	27.34	152/0.5
3-l	2-Cl, 4-Cl-C_6H_3	4	56	24.71	170/0.5

* Calculated for distillated or crystallized products.

TABLE 4

Cycloalkylphosphonate α-sulfides



Entry	R	n	Yield %*	^{31}P-NMR ($CDCl_3$) δ ppm	BP°C/mmHg
4-a		2	74	24.70	80/0.5
4-b	CH_3	3	52	23.43	97/0.5
4-c		4	55	25.76	96/0.3
4-d		5	53	24.18	104/0.4
4-e		2	72	23.05	132/0.4
4-f	C_6H_5	3	53	23.29	135/0.3
4-g		4	55	27.09	152/0.4
4-h		5	48	24.26	158/0.3
4-i	4-CH_3-C_6H_4	5	60	26.71	168/0.3
4-j	4-Br-C_6H_4	5	63	26.63	180/1.5
4-k	4-CH_3O-C_6H_4	5	59	26.79	193/0.5

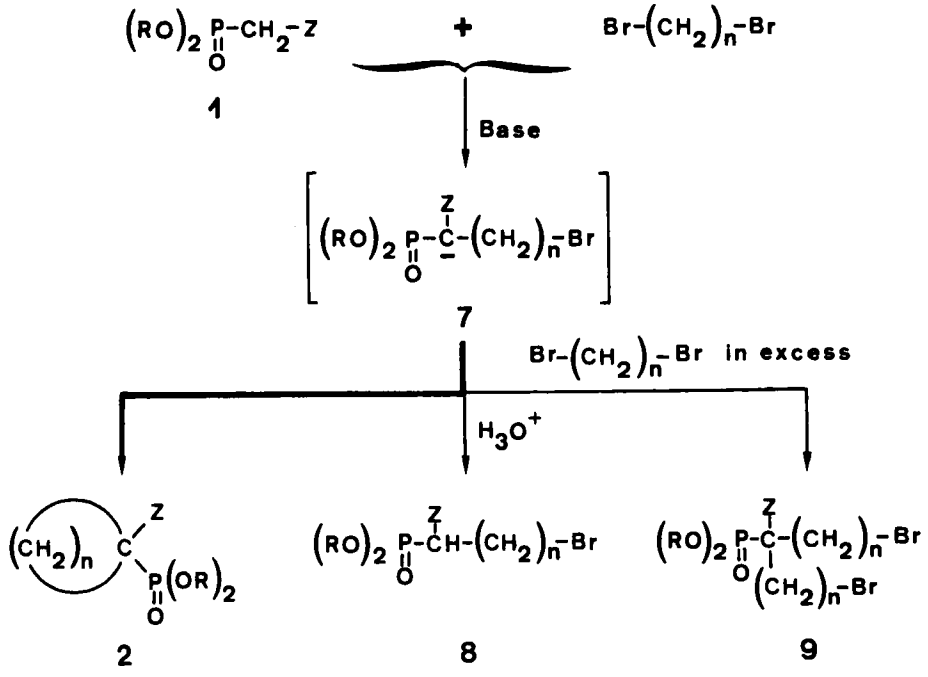
* After distillation.

mined by GC) in neat DMSO, but there was no separation of the starting phosphonate from cyclopropylphosphonate[36] achieved. For $n = 2$ and $n = 3$, the reaction was also incomplete with Z = P(O) $(OC_2H_5)_2$ even in the system *t*-BuOK/DMSO[37]; conversely, α-ethoxycarbonylcyclobutylphosphonate was easily obtained without by-products,[38] using standard conditions of method A.

When Z = aryl or sulfide groups we had to use method C. LDA (in-situ generated from *n*-BuLi and diisopropylamine in THF/hexane) and ω-dibromoalkane were employed in excess (3 and 4 eq., respectively). Metallation of phosphonate **1** and addition of dibromoalkane were carried out at −70°C; then the temperature was left to rise to 20°C. Results relating to these series appear in Tables 3 and 4. For all attempts reported, phosphonate **1** was completely consumed but some degradation of the crude products occurs during distillation. Sometimes, this difficulty was avoided by a prior filtration over silica.

Considering the whole data presented in Tables 1, 2, 3 and 4 it appears that the facility of cyclisation roughly decreases in the following order, according to *n*: $2 > 4 > 5 \geq 3$. This sequence agrees with previously described results recorded in the malonic series.[33]

Besides to the difficulties relating to purification, formation of large cycles ($n > 5$) lacks chemoselectivity. Actually, whatever method we used, the reaction's mechanism includes two steps. The first one leads to an intermediate anion **7** resulting from monoalkylation of **1**. When the geometry is favourable ($n = 2, 4, 5$), this anion cyclised readily giving pure cycloalkylphosphonate **2**. On the other hand, with $n > 5$ and sometimes with $n = 3$, the entropy effect of cyclisation is less



Scheme 3

favourable; consequently the concentration of anion **7** in reaction mixture was not negligible so that phosphonate **8** is present in the crude product after hydrolysis. In addition, anion **7** may undergo a second alkylation by excess of ω-dibromoalkane to give diakylated phosphonate **9** (Scheme 3).

EXPERIMENTAL

Structures were checked by NMR and IR spectroscopies. IR spectra were recorded on a Beckmann 4250 spectrophotometer. ^{1}H-NMR spectra were obtained from a Varian T 60 spectrometer (using TMS as internal reference). ^{31}P-NMR spectra were determined on a Brucker WP 90 spectrometer in reference to H_3PO_4 85%. GC analyses were performed on a Girdel 300 chromatograph. Elemental microanalyses were realized on a Carlo Erba 1106 analyser.

Synthesis of starting phosphonates **1**. Most non-commercially available phosphonates $(RO)_2P(O)\text{-}CH_2\text{-}Z$ were prepared by the classical Arbusov reaction between trialkylphosphites $(RO)_3P$ and the corresponding halides $Cl\text{-}CH_2\text{-}Z$. α-Sulfonylmethylphosphonates were obtained from the relevant α-sulfides by oxidation ($KMnO_4$ in C_6H_6[40]). Results are given as follows: R/Z/pure yield %/^{31}P-δ ppm ($CDCl_3$)/BP°C, mmHg or MP°C, solvent of cryst.: *n*-C_4H_9/CN/95/13.96/116, 0.4[41]; C_2H_5/$(C_2H_5O)_2P(O)$/85/16.73/130, 0.5[42]; C_2H_5/C_6H_5/90/23.13/120, 0.5[43]/C_2H_5/2-Cl-C_6H_4/88/22.45/122, 0.6; C_2H_5/4-Cl-C_6H_4/85/22.90/120, 0.3; C_2H_5/2-Cl, 4-Cl-C_6H_3/93/21.77/101, 1; C_2H_5/3-CH_3O-C_6H_4/87/23.58/135, 0.5; C_2H_5/C_6H_5-S/80/20.20/136, 0.5[44]; C_2H_5/CH_3-S/82/21.70/76, 0.5[43]; C_2H_5/4-CH_3-C_6H_4-S/90/20.49/155, 0.7; C_2H_5/4-Br-C_6H_4-S/85/22.19/180, 0.6[44]; C_2H_5/4-CH_3O-C_6H_4-S/92/20.57/176, 0.7; C_2H_5/CH_3-SO_2/70/8.98/106, benzene; C_2H_5/C_6H_5-SO_2/76/8.30/59, benzene-heptane (1–1).

Synthesis of α-functional cycloalkylphosphonates **2**. We describe the general experimental procedure for each method of cyclisation.

Method A. A mixture of α-functional methylphosphonate **1** (0.02 mol) and ω-dibromoalkane (0.021 mol) was added dropwise at room temperature, with efficient mechanical stirring and under nitrogen to a suspension of NaH (0.042 mol) in THF (50 ml). Few minutes later, an exothermic reaction occurred: temperature rose to 60–70°C and viscosity increased rapidly (sometimes, we had to add more THF to make stirring possible). After returning to room temperature, 4 N HCl was added until pH 1 was reached. After decantation, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml). Organic layers were dried ($MgSO_4$) and the solvents removed under reduced pressure giving the crude product.

Method B. A mixture of phosphonate **1** (0.01 mol) and ω-dibromoalkane (0.025 mol) dissolved in acetonitrile (10 ml) was added dropwise under magnetic stirring to a mixture of dry K_2CO_3 (0.03 mol) and triethylbenzylammonium chloride (TEBAC, 200 mg) in CH_3CN (10 ml). The mixture, protected from moisture, was stirred overnight at 80°C, cooled to room temperature, then filtered. The filtrate was freed from volatile material under reduced pressure to give the crude product. Operations repeated on 0.1 mol of **1**, 0.3 mol of K_2CO_3, 0.25 mol of halide, 450 mg of TEBAC and 100 ml of acetonitrile afforded similar yields.

Method C. A 1.6 molar solution of *n*BuLi (0.06 mol) in hexane was introduced into a flask under nitrogen, then diisopropylamine (0.06 mol) dissolved in THF (10 ml) was added to the cooled solution (−30°C). Ten minutes later, the solution was cooled to −70°C and phosphonate **1** (0.02 mol, in 10 ml THF) was added. The resulting mixture was stirred for 10 min. ω-Dibromoalkane (0.08 mol, in 5 ml THF) was added at −70°C and the mixture slowly allowed to warm to room temperature. The reaction mixture was then acidified with 4 N HCl and decanted. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). Organic layers were dried ($MgSO_4$) and the solvents evaporated in vacuo to give the crude product.

α-Functional cycloalkylphosphonates **2** described in Tables 1, 2, 3 and 4 were characterized by the following supplementary data: ^{1}H-NMR and possibly IR spectra. Moreover, satisfactory (± 0.4%) elemental microanalyses (C, H, N) were obtained for all these compounds.

^{1}H-NMR spectra: In addition to the functional groups [$(RO)_2P(O)$ and Z], that give their usual and well identified bands, the cyclic part [$(CH_2)_n$] appears as a multiplet whose limits vary slightly according to Z and *n*, as follows (δ_{ppm}, in $CDCl_3$): for Z = CN: 1.3 to 1.7 (*n* = 2); 2.0 to 3.1 (*n* = 3); 1.6 to 2.5 (*n* = 4); 1.2 to 2.4 (*n* = 5, 6). For Z = CH_3-SO_2: 1.3 to 1.7 (*n* = 2); 1.9 to 3.2 (*n* = 3); 1.4 to 2.5 (*n* = 4); 1.2 to 2.4 (*n* = 5). For Z = C_6H_5-SO_2: 1.4 to 1.9 (*n* = 2); 1.8 to 3.1 (*n* = 3); 1.4 to 2.6 (*n* = 4); 1.2 to 2.4 (*n* = 5). For Z = $C(O)OC_2H_5$: 1.7 to 2.8 (*n* = 3); 1.2 to 2.8 (*n* = 4, 5). For

Z = $P(O)(OC_2H_5)_2$: 1.3 to 2.5 (n = 4, 5). For Z = Ar: 1.3 to 1.7 (n = 2); 1.5 to 3.0 (n = 3); 1.3 to 2.5 (n = 4); 1.2 to 2.6 (n = 5). For Z = CH_3-S: 0.9 to 1.4 (n = 2); 1.8 to 3.1 (n = 3); 1.4 to 2.6 (n = 4); 1.2 to 2.4 (n = 5). For Z = Ar-S: 1.3 to 1.7 (n = 2); 1.8 to 3.1 (n = 3); 1.3 to 2.5 (n = 4); 1.2 to 2.4 (n = 5).

IR Spectra: IR spectroscopy (neat liquid) was used especially for the nitrile and ester series. For Z = CN, the position of the ν_{CN} band is found at 2260 cm^{-1} (phosphonate **1**) to 2230–2240 cm^{-1} (phosphonate **2**). For Z = $C(O)OC_2H_5$, the ν_{CO} band is found at 1745 cm^{-1}(**1**) to 1725–1730 cm^{-1}(**2**).

CONCLUSION

For most examples reported in this work, cyclisation was the greatly predominant reaction leading to crude products of excellent quality (controlled by GC, ^{31}P- and ^1H-NMR), that may be used for further reactions,[39] after a single filtration over silica. Under these conditions we prepared easily, in one operation, several grams of cycloalkylphosphonates **2** with crude yields in the range from 80 to 95%.

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