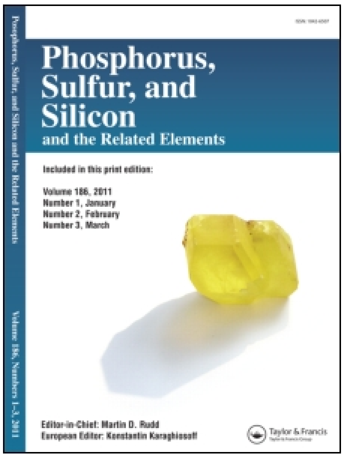

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PHOSPHONIC SYSTEMS. PART 13. ALKYLATION OF DIETHYL CYCLOHEXENYLPHOSPHONATES

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PHOSPHONIC SYSTEMS. PART 13. ALKYLATION OF DIETHYL CYCLOHEXENYLPHOSPHONATES

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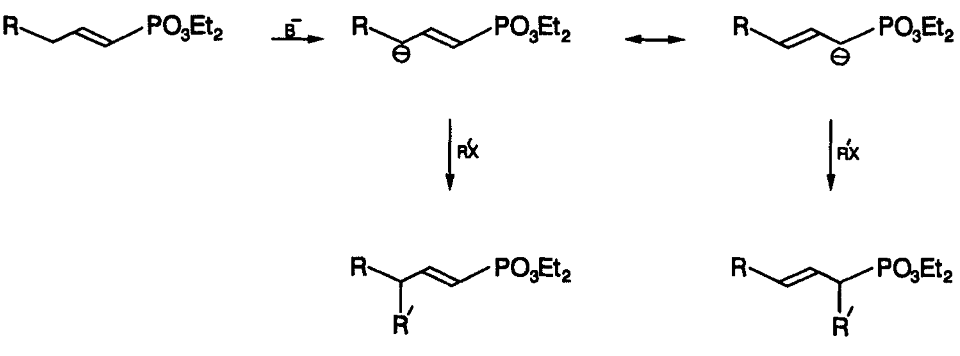
Alkylation of cyclohexenylphosphonates was found to proceed under very mild conditions. The reaction usually occurred in a regioselective fashion with α-addition predominating. Steric effects were significant and had a bearing on the regioselectivity of the reaction.

Key words: Cycloalkenylphosphonic esters; alkylation of allylic phosphonate carbanions; regioselectivity in alkylation.

INTRODUCTION

Alkylation of alkylphosphonate esters allows modification of the carbon skeleton of the reagents. Hence, these reactions have attracted considerable interest over the years.[1-3] Activated phosphonates, such as triethyl phosphonoacetate[4] and cyanomethylphosphonate[5] have been successfully alkylated. Investigations of allylic systems are limited to propenyl-phosphonates[6,7] and some acyclic analogues.[7,8] Alkylation was found to occur mostly at the α-position with respect to phosphorus, even though γ-addition is possible (Scheme 1). To our knowledge, no work has

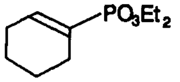


Scheme 1

been done on cycloalkenylphosphonates. Due to ring congestion, these phosphonate carbanions should be less reactive and, hence, more selective than their acyclic analogues. Self condensation reactions[9] would also not be expected to compete efficiently with alkylation for similar reasons.

RESULTS AND DISCUSSION

Diethyl cyclohexen-1-ylphosphonate (**1**) was chosen as the first of three model compounds. Upon deprotonation by an efficient base, a carbanion can result with the negative charge centered at the α- or γ-position with respect to phosphorus. However, only parent phosphonate was recovered after iodomethane or l-bromopropane were added to a solution containing the phosphonate carbanion. Quenching of the reaction mixture with deuterium oxide did not result in deuterium incorporation into the phosphonate, indicating that the failure in alkylation was not due to any steric repulsion between the carbanion and the electrophile. Recent results[10] have indicated, however, that deprotonation of the γ-position in the 1,2-unsaturated isomer is much less facile than abstraction of an α-proton from the 2,3-unsaturated isomer of the phosphonate. Hence, it is possible that the immediate



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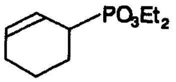

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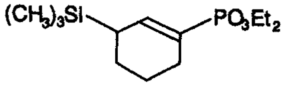

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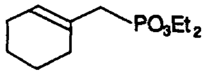

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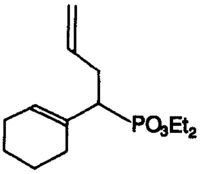


5

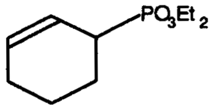
concentration of carbanion was low upon addition of the alkyl halide and, subsequent, reaction between the base and electrophile depleted the base concentration.

Consequently, diethyl cyclohexen-2-ylphosphonate (**2**) was utilised as a substrate. Unlike its cyclohexen-1-yl analogue, a sterically crowded carbanion would result upon deprotonation of the acidic α-position. However, in view of the thermodynamic instability of this carbanion as compared to the 1,2-unsaturated form,[11] enhanced reactivity towards alkyl halides was expected. This was, indeed, found to be the case. Steric factors were found to be less important than anticipated and diethyl cyclohexen-2-ylphosphonate (**2**) could be alkylated by various electrophiles. Results are summarized in Table I. The choice of base was found to be important. Treatment of a solution of the phosphonate at low temperature with butyllithium and subsequent addition of the electrophile afforded the adduct. However, the phosphonate, in the presence of sodium hydride, failed to react with alkyl halides, even at elevated temperatures.

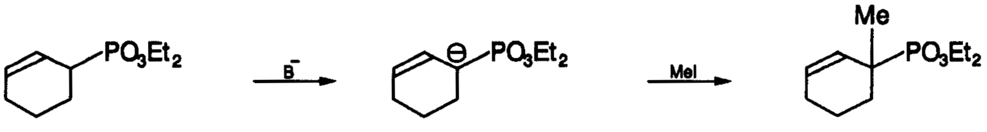
Contrary to the reaction of diethyl cyclohexen-1-ylphosphonate (**1**) with iodomethane, the latter was found to react with cyclohexen-2-ylphosphonate (**2**) nearly quantitatively. Substitution proceeded exclusively at the α-position with respect to phosphorus (Scheme 2). The effect of increasing substitution at the electrophilic centre was found to be insignificant in the reaction of **2** with 1-bromopropane and 3-bromopropene. This indicates that short carbon chains attached to a terminal electrophilic centre do not interfere with the approach of the carbanion. In addition,

TABLE I

Alkylation of 2

Phosphonate	Alkylating agent	Product Yield (%)	
	Iodomethane	92^a	99^b
	1-Bromopropane	89^a	99^b
	2-Bromopropane	45^a	70^b
	3-Bromopropene	72^a	80^b
	Trimethylchlorosilane	34^a	80^b

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra



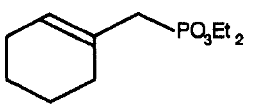
Scheme 2

the effect of the leaving group was negligible since the less reactive alkyl bromides reacted to a similar extent as iodomethane. The size effect did become evident when a secondary alkyl halide was used. The yield of adduct decreased when 2-bromopropane was added to a mixture of diethyl cyclohexen-2-ylphosphonate (**2**) and butyllithium. Material balance consisted of unreacted phosphonate as well as diethyl cyclohexen-l-ylphosphonate **1** (product of isomerisation of **2**). Hence, it was deemed interesting to investigate the reaction of **2** with a bulky reagent, such as chlorotrimethylsilane. Diethyl (3-tri-methylsilyl)cyclohexen-1-ylphosphonate (**3**) was isolated as the major product of the reaction mixture. Due to steric congestion of the lithiated α-position and bulk of the electrophile, isomerisation of the double bond and subsequent substitution at the γ-position predominated. The reason for the unreactive 1,2-unsaturated isomer being trapped by chlorotrimethylsilane, whereas iodomethane failed to react, is possibly due to a unimolecular reaction mechanism operating in the case of the former due to the instability of the silicon-chlorine bond.[12]

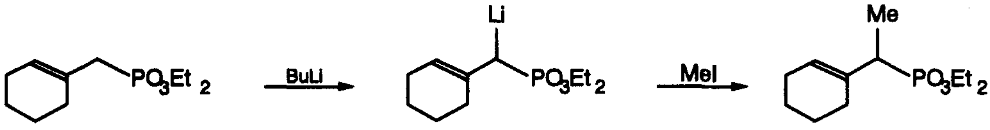
Diethyl cyclohexen-1-ylmethylphosphonate (**4**) was also selected as a substrate since in this reagent, the olefinic bond is situated in the β,γ-position with respect to phosphorus, similar as in diethyl cyclohexen-2-ylphosphonate (**2**). However, an advantage over the latter is its relative thermodynamic stability[11] and uncongested α-carbon. The nucleophilic centre should, thus, be more accessible to bulky electrophiles. In addition, competitive isomerisation to the unreactive 1,2-unsaturated isomer should not occur to a significant extent. Results of the alkylations of **4** are tabulated in Table II.

Iodomethane was again used as electrophile to compare the nucleophilicity of **4** with its cyclohexen-2-yl analogue **2**. As for reactions of the latter, yields were nearly quantitative and reaction occurred exclusively α with respect to phosphorus (Scheme 3). l-Bromopropane also afforded α-product in high yield. However, the reaction was partially retarded when 2-bromopropane was used as electrophile. Although the yield was higher than for the corresponding cyclohexen-2-ylphosphonate **2**, a considerable amount of parent phosphonate was recovered. The lower yield of adduct can also be attributed to the lower reactivity of the electrophile, though, it would not be expected to have such a dramatic effect. 3-Bromopropene again

TABLE II
Alkylation of 4

Phosphonate	Alkylating agent	Product Yield (%)	
	Iodomethane	93[a]	95[b]
	1-Bromopropane	87[a]	99[b]
	2-Bromopropane	65[a]	75[b]
	3-Bromopropene	80[a]	95[b]

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra



Scheme 3

reacted to afford the product (**5**) in high yield. The latter is interesting in that two reactive allylic centres are present in the molecule. Hence, treatment of (**5**) with base can be envisaged to result in competitive abstraction of the proton α, and those β, with respect to phosphorus.

The information on the reactivity and regioselectivity of alkylation of cycloalkenylphosphonates lies a valuable foundation for other addition reactions. For example, the adducts obtained from aldehyde addition reactions are used as precursors of dienes.[13,14] In addition, alkylation of phosphonates allows carbon skeleton modification of the substrate which is an added advantage over the analogous Wittig procedure for diene preparation. Diene formation from these aldehyde addition reactions will be the topic of a following paper.

EXPERIMENTAL

All compounds prepared, were fully characterised using high resolution (300 MHz) ^{1}H, ^{13}C and ^{31}P NMR, as well as infrared spectroscopy and mass spectrometry. Purification of products was accomplished by column (silica gel 60, ethyl acetate/hexane) chromatography. The preparation of compounds **1**, **2** and **4** was described in a previous paper.[11]

General procedure for alkylation. The phosphonate (5 mmol) in dry THF, under a nitrogen atmosphere, was cooled to −78°C whereupon a solution of butyllithium (1.6 M solution in hexane; 6–8.5 mmol) was added dropwise. After stirring for 1 h, the corresponding electrophile (8 mmol) was added slowly and stirred continuously at −78°C for 30 min. The reaction mixture was allowed to reach ambient temperature and kept for 1 h. Subsequent washing with aqueous ammonium chloride solution, extraction with methylene dichloride, drying and concentration afforded the crude product which was purified by chromatography. Properties, as well as spectral and analytical data for each product, are reported below for the individual syntheses. In all cases, yields of isolated products, as well as those based upon ^{31}P NMR spectra, are reported.

(A) Alkylation of diethyl cyclohexen-1-ylphosphonate (**1**).

(i) With iodomethane and 1-bromopropane. Diethyl cyclohexen-1-ylphosphonate (1.03 g; 4.72 mmol) and butyllithium (3.50 ml; 5.60 mmol) in dry THF were treated at −78°C with iodomethane (1.07 g; 7.56 mmol) and stirred at ambient temperature for 1–4 h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-1-ylphosphonate (0.93 g; 4.26 mmol; 90.2%), identical (^{31}P, ^{1}H NMR spectra and TLC) to an authentic sample. An identical result was obtained when 1-bromopropane was used.

(B) Alkylation of diethyl cyclohexen-2-ylphosphonate (**2**). The following products were prepared:

(i) Diethyl 1-methylcyclohexen-2-ylphosphonate, purified by chromatography (flash column, hexane/ethyl acetate, 4:1) and distillation, b.p. (oven temp.) 110°C/0.2 mbar; (91.7% [99]); δ_H ($CDCl_3$) 1.22 (3H, d, J_{HP} 16.9 Hz), 1.28 (6H, t, J_{HH} 7.1 Hz), 1.50 (2H, m), 1.83 (1H, m), 1.90 (3H, m), 4.07 (4H, q, $J_{HH} = J_{HP}$ 7.1 Hz), 5.57 (1H, m), 5.80 (1H, m). δ_P 33,55. MS m/z 232 (M^+, 37%), 139 (53), 111 (27), 94 (100), 79 (35).

(ii) Diethyl 1-propylcyclohexen-2-ylphosphonate, purified as above, b.p. (oven temp.) 135.0°C/0.2 mbar (89.0% [99]); δ_H ($CDCl_3$) 0.86 (3H, t, J_{HH} 7.1 Hz), 1.26 (6H, t, J_{HH} 7.1 Hz), 1.30 (2H, m), 1.58 (4H, m), 1.95 (4H, m), 4.05 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 5.52 (1H, m), 5.89 (1H, m, J_{HP} 14.2 Hz; J_{HH} 4.0 Hz). δ_P 33.06. MS m/z 260 (M^+, 51%), 231 (10), 220 (20), 191 (19), 139 (53), 122 (100), 111 (35), 79 (48).

(iii) Diethyl 1-(1′-methylethyl)-cyclohexen-2-ylphosphonate, purified as above, b.p. (oven temp.) 135.0°C/0.2 mbar (45.0% [70]); δ_H ($CDCl_3$) 0.87 (3H, d, J_{HH} 6.9 Hz), 1.00 (3H, d, J_{HH} 6.9 Hz), 1.26 (6H, t, J_{HH} 7.1 Hz), 1.58 (2H, m), 1.93 (4H, m), 2.10 (1H, sept, J_{HH} 6.9 Hz, J_{HP} 19.7 Hz), 4.05 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 5.48 (1H, m), 5.90 (1H, m, J_{HP} 14.3 Hz, J_{HH} 4.1 Hz). δ_P 32,88. MS 260 (M^+, 74%), 245 (20), 218 (61), 190 (22), 162 (38), 139 (51), 122 (100), 111 (33), 79 (79).

(iv) Diethyl 1-(propen-2′-yl)cyclohexen-2-ylphosphonate, purified by column chromatography (hexane/ethyl acetate, 7:3) (decomposes upon distillation at 140°C/0.3 mbar) (71.9% [80]); δ_H ($CDCl_3$) 1.27 (6H, t, J_{HH} 7.1 Hz), 1.57 (2H, m), 1.95 (4H, m), 2.40 (2H, m, J_{HH} 6.5 Hz), 4.05 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 5.00 (2H, d, J_{HH} 12.6 Hz), 5.52 (1H, m), 5.75 (1H, m), 5.90 (1H, m, J_{HH} 4.0 Hz, J_{HP} 14.1 Hz). δ_P 31.09. MS 259 (M^+, 100%), 217 (85), 161 (19), 139 (55), 120 (93), 111 (52), 91 (99), 79 (99).

(v) Diethyl 3-trimethylsilylcyclohexen-1-yl-phosphonate (**3**), purified by chromatography (flash column, hexane/ethyl acetate, 4:1) (decomposes upon distillation) (33.5% [80]). ν_{max} ($CHCl_3$) 1617 cm^{-1}. δ_H ($CDCl_3$) 0.01 (9H, s), 1.27 (6H, t, J_{HH} 7.1 Hz), 1.45 (2H, m), 1.73 (3H, m), 2.05 (2H, m), 4.05 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 6.79 (1H, d, J_{HP} 22.4 Hz). δ_P 21.62 δ_C (DEPT) $-$ 3.2 (3 × Me), 16.1 (2 × Me), 21.5 (CH_2), 22.6 (CH_2), 24.0 (CH_2), 28.3 (CH), 61.0 (2 × CH_2), 145.3 (CH). MS m/z 218 (100%), 190 (25), 162 (33), 79 (18).

(C) Alkylation of diethyl cyclohexen-1-ylmethylphosphonate (**4**). The following products were prepared:

(i) Diethyl 1-methylcyclohexen-1-ylmethylphosphonate, purified by column chromatography (hexane/ethyl acetate, 7:3) and distillation, b.p. (oven temp.) 120°C/0.2 mbar (93.4% [95]). δ_H ($CDCl_3$) 1.21 (3H, dd, J_{HH} 7.6 Hz, J_{HP} 18.5 Hz), 1.27 (6H, t, J_{HH} 7.1 Hz), 1.54 (4H, m), 2.01 (4H, m), 2.45 (1H, dq, J_{HH} 7.4 Hz, J_{HP} 22.9 Hz), 4.02 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 5.59 (1H, br s). δ_P 31.74. MS m/z 246 (M^+, 48%), 231 (12), 138 (30), 108 (100), 93 (22), 79 (33).

(ii) Diethyl 1-propylcyclohexen-1-ylmethylphosphonate, purified as above, b.p. (oven temp.) 130°C/0.2 mbar (87.2% [99]). δ_H ($CDCl_3$) 0.81 (3H, t, J_{HH} 7.1 Hz), 1.24 (6H, t, J_{HH} 7.1 Hz), 1.25 (2H, m), 1.58 (6H, m), 1.95 (4H, m), 2.34 (1H, dt, J_{HH} 7.1 Hz, J_{HP} 22.8 Hz), 3.98 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 5.53 (1H, br s). δ_P 31.18. MS m/z 274 (M^+, 96%), 232 (75), 136 (100), 107 (66), 95 (47), 79 (45).

(iii) Diethyl-1-(propen-2′-yl)cyclohexen-1-ylmethylphosphonate (**5**), purified as above, b.p. (oven temp.) 130°C/0.2 mbar (80.2% [95]). δ_H ($CDCl_3$) 1.21 (3H, t, J_{HH} 7.1 Hz), 1.22 (3H, t, J_{HH} 7.1 Hz), 1.48 (4H, m), 1.95 (4H, m), 2.40 (3H, m), 4.00 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 4.88 (1H, d, J_{HH_c} 10.0 Hz), 4.94 (1H, d, J_{HH_t} 17.0 Hz), 5.53 (1H, br s), 5.61 (1H, m). δ_P 30.05. δ_C 16.2 (2 × Me, q, J_{CH} 127.1 Hz), 22.0 (CH_2, t, J_{CH} 127.8 Hz), 22.7 (CH_2, t, J_{CH} 127.5 Hz), 25.3 (CH_2, t, J_{CH} 121.9 Hz), 27.4 (CH_2, t, J_{CH} 128.0 Hz), 31.6 (CH_2, t, J_{CH} 128.1 Hz), 45.6 (CH, dd, J_{CH} = J_{CP} 130.3 Hz), 61.3 (2 × CH_2, t, J_{CH} 147.0 Hz), 115.9 (CH_2, t, J_{CH} 157.7 Hz), 126.6 (CH, d, J_{CH} 154.0 Hz), 131.5 (C, s), 135.8 (CH, d, J_{CH} 152.1 Hz). MS m/z 272 (M^+, 22%), 231 (26), 134 (100), 91 (42), 79 (19).

(iv) Diethyl 1-(1′-methylethylcyclohexen-1-ylmethylphosphonate, purified by column chromatography (dichloromethane) and distillation, b.p. (oven temp.) 140°C/0.4 mbar (64.6% [77]). δ_H ($CDCl_3$) 0.82 (3H, d, J_{HH} 6.4 Hz), 1.02 (3H, d, J_{HH} 6.4 Hz), 1.20 (3H, t, J_{HH} 7.1 Hz), 1.21 (3H, t, J_{HH} 7.1 Hz), 1.50 (4H, m), 1.98 (5H, m), 3.97 (4H, q, J_{HH} = J_{HP} 7.1 Hz), 5.53 (1H, br s). δ_P 30.67. MS m/z 274 (M^+, 32%), 259 (5), 231 (83), 203 (41), 175 (49), 136 (90), 93 (91), 81 (91), 41 (100).

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