

NOVEL AND EFFICIENT SYNTHESIS OF URACIL PHOSPHONATE DERIVATIVES VIA PENTACOVALENT OXAPHOSPHOLENES

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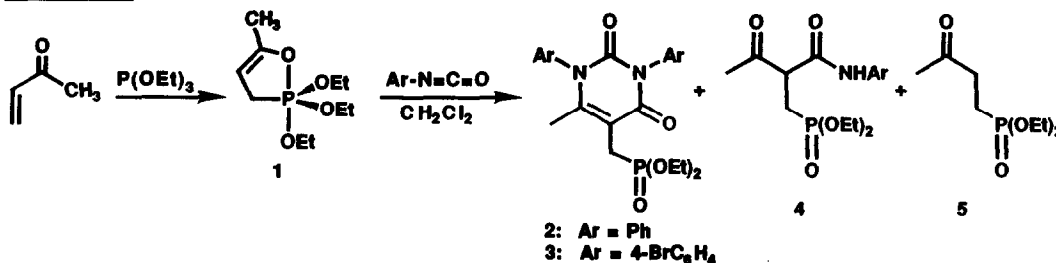
ABSTRACT: 2,2,2-Triethoxy-1,2λ⁵-oxaphospholene, **1**, reacts under mild, neutral conditions with aryl isocyanates to produce the phosphonate-containing pyrimidinedione derivatives **2** and **3**. X-ray structure determination of **3** confirmed its structure.

Keywords: Pentacovalent oxaphospholenes, C-nucleosides, phosphonates, isocyanates, pyrimidinedione.

Since naturally occurring C-nucleosides exhibit impressive antitumor and antiviral properties, there has been a great deal of interest in producing *synthetic* C-nucleoside analogues of the N-connected bases and nucleosides.³ Heterocyclic phosphonate derivatives have recently been shown to be valuable intermediates in the syntheses of C-nucleosides.⁴ Some of these heterocyclic phosphonates also display biological activity themselves.⁵ We now present an extremely efficient and novel *two-step* synthesis of the methylphosphonate pyrimidinedione derivatives **2** and **3**.

While investigating reactions of pentacovalent oxaphospholenes with electrophiles,⁶ we discovered that **1** reacted readily with isocyanates to produce the double addition products **2** and **3** in excellent isolated yields (92% and 93%, respectively).⁷ The oxaphospholene **1** can be

Scheme 1



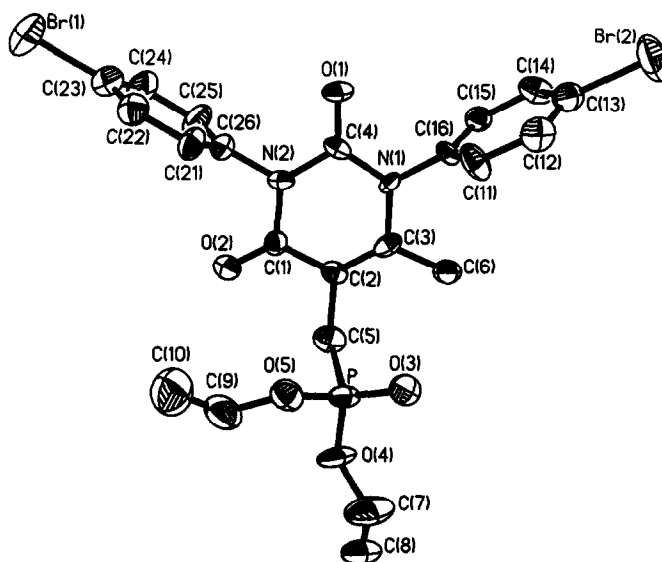
produced on 30-50 g scale and will keep for months if stored in a freezer under argon. The condensation of **1** with the requisite isocyanate proceeded readily at room temperature in CH_2Cl_2 .⁸ The use of only one equivalent of phenyl isocyanate led to a mixture of the heterocycle **2**, the amide **4** and hydrolysis product **5**, with the double addition product being major (Table 1). Utilization of two equivalents of the isocyanate produced **2** in 92 % isolated yield as a crystalline solid, with only minor amounts of **4** and **5** being formed.

Table 1

Equiv. Ph-NCO	% 2	% 4	% 5
1.0	57.0	10.4	25.6
2.0	92.4	2.2	3.9

In order to conclusively prove its structure, the 4-bromophenyl derivative, **3**, was subjected to single crystal X-ray crystallographic analysis.⁹ The ORTEP representation of the crystal structure is shown in Figure 1. The pyrimidinedione ring was found to be slightly puckered.

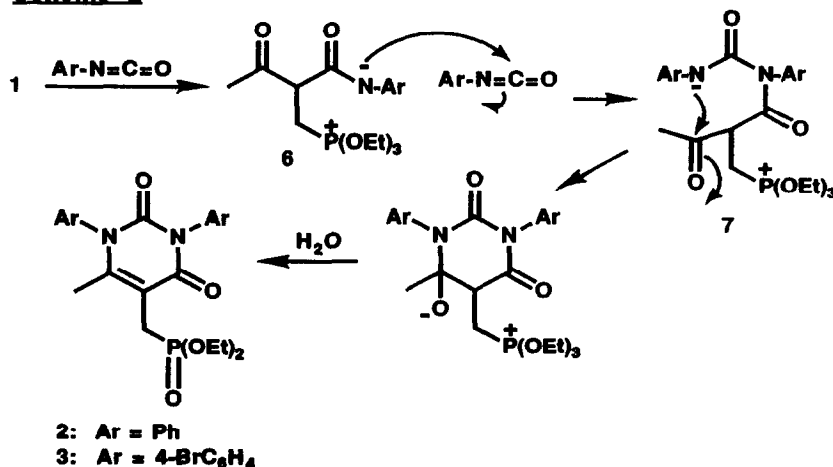
Figure 1



A possible mechanism for this reaction is illustrated in Scheme 2. With 2 equivalents of isocyanate present, the intermediate nitrogen anion in **6** attacks another molecule of isocyanate. The new, incipient nitrogen anion in **7** then attacks the ketone carbonyl to cyclize to the six-

membered ring as shown. Dehydration to the alkene and hydrolysis to the phosphonate leads to the heterocycle.

Scheme 2



In conclusion, we report a novel two step method to produce pyrimidinedione methylphosphonate derivatives using the electrophilic condensation reactions of a pentacovalent oxaphospholene with isocyanates. The use of 4-methoxyphenyl isocyanate to produce pyrimidinedione derivatives with labile groups on the nitrogens,¹⁰ as well as applications to the syntheses of C-nucleosides and antibiotics such as sparsomycin,¹¹ are the subjects of forthcoming papers.

Acknowledgement. We thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Procter & Gamble University Exploratory Research Program for partial support of this research.

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 7. All new compounds exhibited spectroscopic data in agreement with assigned structures.
 8. Preparation of diethyl [(1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-1,3-diphenyl-5-pyrimidinyl)-methyl]-phosphonate **2**: The oxaphospholene **1** (335 mg, 1.42 mmol) was transferred via cannula into a flame-dried flask under Ar and dissolved in freshly distilled CH_2Cl_2 (2 mL). To the flask, freshly distilled phenylisocyanate (0.31 mL, 2.83 mmol) was added dropwise via syringe. The reaction was allowed to stir at rt for 48 hr. During this time, the reaction turned slightly yellow. After 48 hours, the ^1H NMR of the reaction mixture indicated that the oxaphospholene was consumed. The reaction was then hydrolyzed using distilled H_2O (5.0 mL) and stirred for 16 hr at rt. The reaction mixture was extracted using CH_2Cl_2 (3 x 25 mL), and the combined extracts were dried over anhydrous MgSO_4 , filtered, and the solvent removed in vacuo. The residue was eluted through a glass fritted funnel containing approximately 10 g course silica gel washing with CH_2Cl_2 (100 mL) and then with 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (250 mL). The 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ fractions were concentrated under reduced pressure. From this residue, the pyrimidinedione **2** (562 mg, 92.4% yield), keto-amide **4** (10.3 mg, 2.2% yield), and diethyl 3-oxobutylphosphonate **5** (12.4 mg, 3.9% yield) were isolated via separation by HPLC (1.75% $\text{MeOH}/\text{CH}_2\text{Cl}_2$; flow rate: 10 mL/minute; $\lambda_{\text{max}} = 300$ nm). Upon standing, the keto-amide and the pyrimidinedione crystallized, and each compound was independently recrystallized from CH_2Cl_2 via vapor diffusion of pentane. **2**: m.p. = 118°C; R_f (4% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) = 0.28; HPLC Retention Time: 27.1 minutes; ^1H NMR (CDCl_3): 7.50-7.22 (10H, m), 4.15 (4H, apparent pent, $J = 7.1$ Hz), 3.14 (2H, d, $J_{\text{P-H}} = 20.3$ Hz), 2.06 (3H, d, $J_{\text{P-H}} = 3.3$ Hz), 1.30 (6H, t, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3): 162.3, 151.3, 150.5 (d, $J_{\text{P-C}} = 6.9$ Hz), 137.2, 135.1, 129.7, 129.2, 129.1, 128.6, 128.5, 128.1, 103.7 (d, $J_{\text{P-C}} = 9.6$ Hz), 62.2 (d, $J_{\text{P-C}} = 6.4$ Hz), 23.4 (d, $J_{\text{P-C}} = 141.7$ Hz), 18.9, 16.3 (d, $J_{\text{P-C}} = 6.4$ Hz); ^{31}P NMR (CDCl_3): 27.40 ppm; IR (cm^{-1} , CH_2Cl_2): 1712, 1663, 1660, 1490, 1245, 1240, 1075, 1042; Exact mass calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_5\text{P}$: (M) $^+$ 428.1499, found 428.1471.
 9. Compound **3** crystallized in the monoclinic space group $\text{P}2_1/\text{c}$ with $a = 11.925(3)$ Å, $b = 7.817(2)$ Å, $c = 26.758(8)$ Å, $\beta = 90.95(3)^\circ$ and $V = 2494.0(9)$ Å 3 . For $Z = 4$ and $\text{FW} = 586.2$, the calculated density is 1.561 g/cm 3 . The data were collected at 25 ± 1 °C using the Wyckoff scan technique to a maximum 2θ value of 42° . A total of 3001 reflections was collected. The linear absorption coefficient for Mo K_α is 35.0 cm $^{-1}$. An empirical absorption correction, based on azimuthal scans of several reflections was applied. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1391 reflections ($F > 4.0\sigma(F)$) and converged to a final discrepancy factor of $R = 6.49$ % ($R_w = 6.94$ %).
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(Received in USA 9 October 1992)