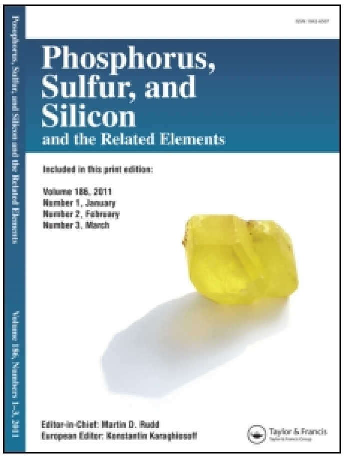

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Investigations of the Reaction of Pentacovalent Oxaphosphlenes with Isocyanates. Synthetic and Mechanistic Aspects

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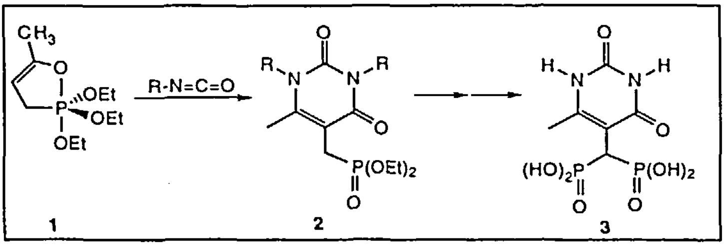
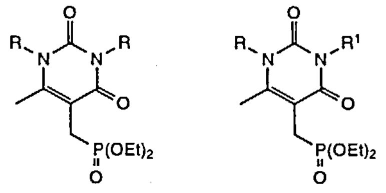
The reaction of the pentacovalent oxaphospholene **1** with isocyanates to produce the heterocycle **2** was followed by NMR in order to delineate the mechanism. The addition of 1 and 2 eq. of an isocyanate to **1** indicated very fast formation of 2 long-lived species that slowly rearranged to product. Cross-over experiments using 2 different isocyanates indicated the very fast formation of a statistical mixture of all 4 products **4–7**. Kinetic analysis of the data was performed.

Keywords: pentacovalent oxaphospholene; pyrimidinedione; phosphonate; isocyanates

We have investigated the mechanism of the condensation of the pentacovalent oxaphospholene **1** with isocyanates[2], as information regarding the possible utilization of two different isocyanates to produce differently protected nitrogens on the heterocycle was desired. The ultimate target is the bisphosphono-heterocycle **3**, a possible inhibitor of bone resorption.[3]



Several experiments were performed to delineate the mechanism, with the reactions being followed by ^1H and ^{31}P NMR. The first experiment consisted of adding 1.0 equivalents of an isocyanate (p-methoxy-phenylisocyanate, PMP-NCO) twice in a sequential fashion, and the reaction observed by NMR. The starting P(V), **1**, was not totally consumed until the second equivalent of isocyanate was added. In the second reaction, 2 equivalents of PMP-NCO was added in one portion to the P(V), and again observed by NMR. The starting P(V) was consumed very quickly. Two crossover experiments were also performed. In the first one, 1.0 eq. of PMP-NCO was added to a solution of **1**, followed by addition of 1.0 equiv. of phenyl-isocyanate several hours later. The products identified were **4** and **5** in a 1:1 ratio (^1H and ^{31}P NMR), where each heterocycle was derived from only one type of isocyanate. When a 1:1 mixture of phenylisocyanate and p-methoxyphenylisocyanate was added to one equivalent of P(V) **1**, 4 products were obtained: the N,N'-diphenyl heterocycle **4**, the N,N'-di-*p*-methoxyphenyl heterocycle **5**, and a 1:1 mixture of the crossover products, **6** and **7**. The ratio of the products obtained was 1:2:1, **4** : (**6** + **7**) : **5**.

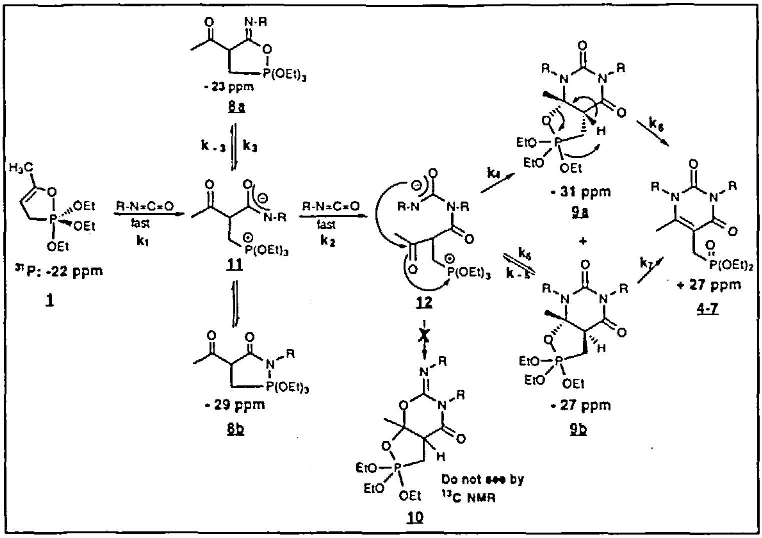


4: R = Ph
5: R = p-MeO-C_6H_4-
6: R = Ph; R^1= p-MeO-C_6H_4-
7: R = p-MeO-C_6H_4-; R^1= Ph

We propose the mechanism and intermediates shown in **Scheme 1**. Thus, rapid reaction between the P(V) **1** and 1 eq. of isocyanate occured to produce small amounts of the transient mono-addition intermediates at -23 and -29 ppm (**8a** and **8b**). These then reacted very rapidly with another molecule of isocyanate to produce the heterocyclic P(V)'s **9a** and **9b** (-31 and -27 ppm). The intermediate P(V)'s **9a** and **9b** slowly rearranged to form the product heterocycles, **4**, **5**, **6** &/or **7**. When only one equivalent of isocyanate was available for reaction, a large amount of starting P(V) **1** was still present, as the pool of isocyanate was depleted very rapidly. The intermediates **9a** and **9b** contain the same R groups on both nitrogens under these conditions. Upon addition of another equivalent of isocyanate, the residual starting P(V) **1** reacted quickly to produce the bis-addition product intermediates, **9a** and **9b**, where the R groups on the nitrogens were also identical on those intermediates.

In the cross-over experiment, a 1:1 mixture of the two different isocyanates was added to the P(V) **1**. In this case, a statistical mixture of the 4 possible products was obtained (1:2:1, **4** : (**6** + **7**) : **5**). That the new, long-lived, intermediate P(V) species, **9a** and **9b**, did not contain an olefin (as in the final heterocyclic product) was illustrated by ^{13}C NMR data. We have also ruled out the possiblity of the minor P(V) intermediate species at -27 ppm being due to the heterocycle **10** (formed by addition of the nitrogen anion onto the ketone carbonyl) by ^{13}C NMR data.

Scheme 1



The kinetics of the reactions were modelled by using fifth order Runge-Kutta methods to solve the following coupled differential equations. In the early kinetic runs, only a reasonable fit to the data was found. We are continuing to refine the kinetic analysis.

Isc = isocyanate; P = compounds 4-7.

$\partial[1]/\partial t = -k_1[1][Isc]$

$\partial[Isc]/\partial t = -k_1[1][Isc] - k_2[11][Isc]$

$\partial[11]/\partial t = k_1[1][Isc] - k_2[11][Isc] - k_3[11] + k_{-3}[8a]$

$\partial[8a]/\partial t = k_3[11] - k_{-3}[8a]$

$\partial[12]/\partial t = k_2[11][Isc] - (k_2 + k_5)[12] - k_{-5}[9b]$

$\partial[9a]/\partial t = k_4[12] - k_6[9a]$

$\partial[9b]/\partial t = k_5[12] - k_7[9b] - k_{-5}[9b]$

$\partial[P]/\partial t = k_6[9a] - k_7[9b]$

$k_1 = 2.3 \times 10^{-4}$
$k_2 = 2.0 \times 10^{-3}$
$k_3 = 1.0 \times 10^{-2}$
$k_{-3} = 2.6 \times 10^{-3}$
$k_4 = 1.1 \times 10^{-1}$
$k_5 = 6.0 \times 10^{-2}$
$k_{-5} = 1.9 \times 10^{-4}$
$k_6 = 1.0 \times 10^{-5}$
$k_7 = 4.0 \times 10^{-9}$

It was found that in order for the data to fit the model, the formation of the intermediate **9b** from **12** had to be a reversible reaction. The major intermediate, **9a**, rearranged to the product at a faster rate than **9b** as it posseses the anti stereochemistry needed for elimination to the alkene. Therefore, since k_2 is greater than k_3 by an order of magnitude, and k_4 or $k_5 > k_2$, two different isocyanates cannot be used to produce the heterocycle with differentially protected nitrogens in any useful yield. When two different isocyanates are utilized in the condensation, mixtures of either cross-over products (**4-7**), or heterocycles containing the same group on the nitrogen (**4**, **5**) are produced.

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