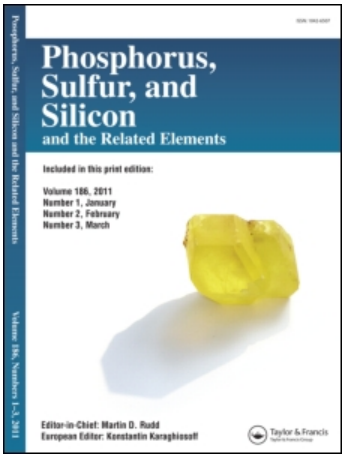

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Pentacovalent Phosphorus in Organic Synthesis: A New Route to Substituted Phosphonates

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PENTACOVALENT PHOSPHORUS IN ORGANIC SYNTHESIS: A NEW ROUTE TO SUBSTITUTED PHOSPHONATES.

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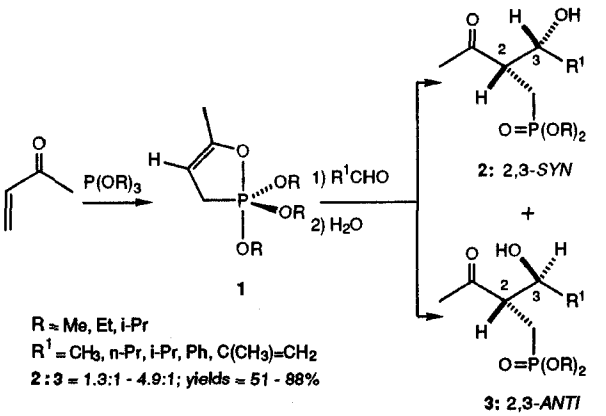
Abstract The pentacovalent oxaphospholene derived from methyl vinyl ketone and trialkyl phosphite has been shown to condense with a variety of electrophiles to produce highly substituted phosphonates.

Highly substituted phosphonates are potential analogues of biologically-active phosphate-containing compounds, as well as valuable synthetic intermediates. The Ramirez condensation reaction[1] is currently being investigated in our group to produce these phosphonates. To date, we have been successful in condensing under *totally neutral conditions* simple 1,2λ^5-oxaphospholenes derived from enones and trialkyl phosphites with aldehydes, azo-diesters, oxaziridines, bromine, acyl chlorides and aryl isocyanates.

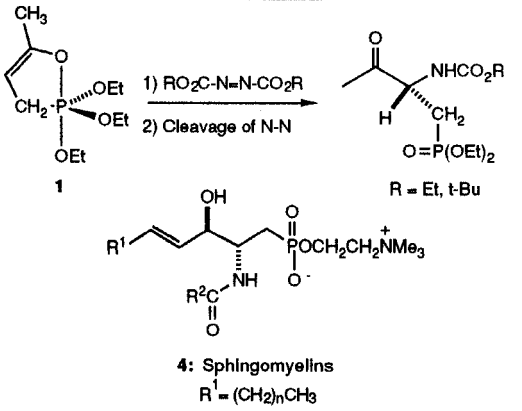
Our initial study on the condensations of the simple oxaphospholenes **1** with 5 different aldehydes produced the variously substituted phosphonates **2** and **3**.[2] We attempted to improve the diastereoselectivity of this reaction by altering reaction conditions (temperature, solvents), and by using various Lewis acids as catalysts. Only the size of the alkyl group on the aldehyde or the phosphite had any effect on the ratio of diastereomers. We are presently investigating this condensation with more highly substituted enones, aldehydes and phosphites. We are also varying the electronegativity of the groups on the enone and the P(III) component to look for any electronic effects on the diastereoselectivity.

Scheme I



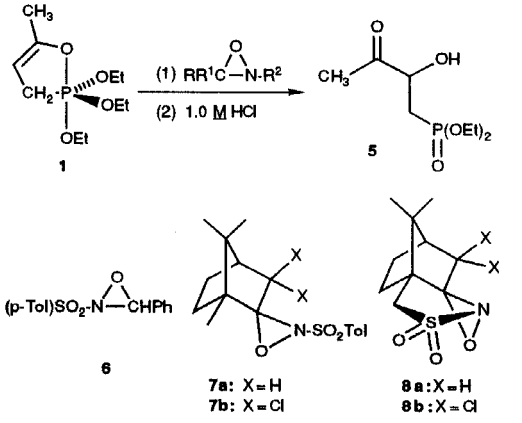
The use of dialkyl azodicarboxylates in the condensation reaction with the enone-phosphite adducts, 1,2λ^5-oxaphospholenes, has the potential to form α-amino phosphonates.[3] We have been successful in condensing **1** with diethyl and di-t-butyl azodicarboxylates. See Scheme II. We are presently investigating methods for reducing the hydrazides to amides. Application of this method will be to the syntheses of non-isoteric phosphonate analogues of the sphingomyelins, **4**. We have been successful in forming the pentacovalent oxaphospholene from *E*-3-oxo-1,4-hexadiene at the least substituted olefin. The reactivity of this P(V) toward electrophiles is currently being investigated.

Scheme II



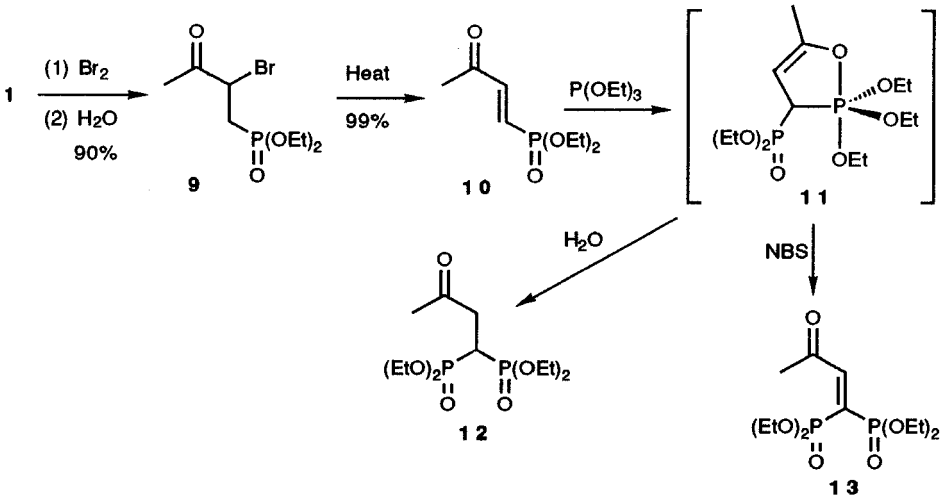
The condensation of **1** with the achiral oxaziridine[4] **6** produced the β-hydroxy γ-ketophosphonate **5** in 82 % isolated yield.[5] See Scheme III. Use of the chiral oxaziridines **7,8** produced **5** in 2-49% ee and 70-95 % yield.[5] The best enantiomeric excess (49%) was with **8b**. We are continuing to search for a better chiral oxaziridine. This reaction allows us quick access to derivatives of 3-phosphono-D-glyceric acid, known enzyme antimetabolites.

Scheme III



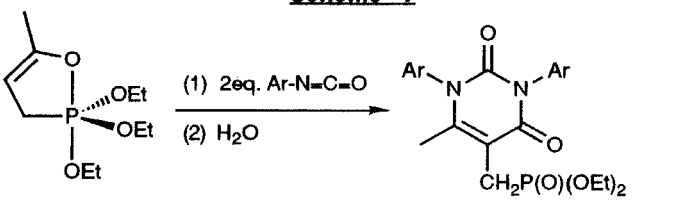
The use of bromine as the electrophile in the condensation with **1** produced the β-bromo γ-keto-phosphonate, **9**, in excellent yield.[5] Heating **9** eliminated HBr to produce the vinyl phosphonate **10** (Scheme IV). The Diels-Alder reaction readily occurs between **10** and cyclopentadiene. We plan to use Diels-Alder reactions to produce phosphonate analogues of carbohydrates, including derivatives of *myo*-inositol phosphates. The bis-phosphonates **12** and **13** can be formed from via the P(V), **11**, by either quenching with water, or reaction with NBS, respectively.

Scheme IV



An interesting thymine derivative, **14**, is the product from the reaction of **1** with aryl isocyanates (Scheme V). X-ray crystallographic studies of both **14a** and **14b** confirmed their structures. The aryl group on **14c** should be able to be oxidatively removed using CAN. This compound will be used in syntheses of nucleotide analogues.

Scheme V

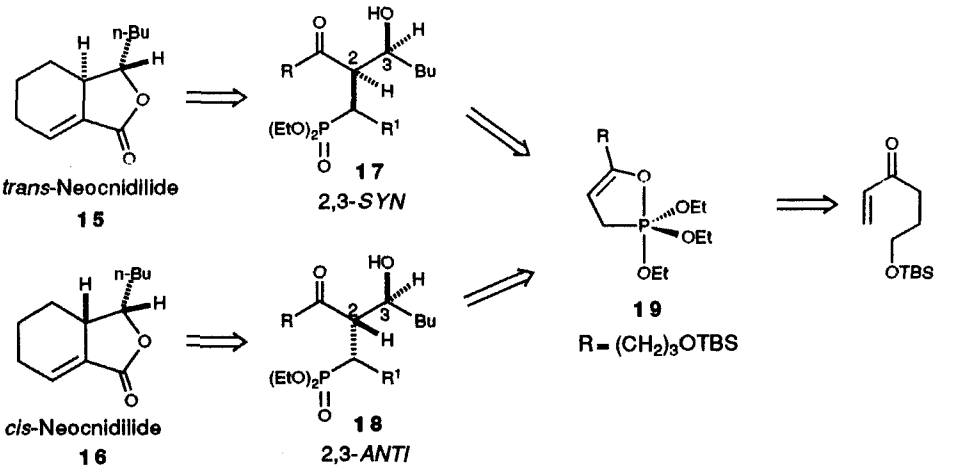


14a: Ar = Ph (92%)
14b: Ar = 4-Br-C_6H_4 (93%)
14c: Ar = 4-MeO-C_6H_4 (90%)

If acyl chlorides are allowed to react with **1**, a mixture of O-acylated and C-acylated products result. We are currently trying to optimize this condensation reaction to produce exclusively one product or the other.

This carbonyl condensation method has also been successfully utilized in the total syntheses of the antibiotics *trans*- and *cis*-neocnidilides, **15** and **16**.[6] See Scheme VI. The key intermediates, highly functionalized phosphonates **17** and **18**, were readily prepared from the condensation of the 1,2λ^5-oxaphospholene **19** with valeraldehyde. *Trans*-neocnidilide was then produced from the syn isomer **17**, and *cis*-neocnidilide from the anti isomer **18**, where the phosphonate functionality was used in an intramolecular Horner-Emmons olefination reaction to form the desired cyclohexene ring.

Scheme VI



We are continuing to try to improve the scope of these reactions, and to screen new electrophilic reagents in the condensation with **1**. Application of this method to the syntheses of phosphonate analogues of bio-active organophosphate compounds will be pursued in the future.

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