PRACTICAL SYNTHESIS OF ALKENYL PHOSPHORUS COMPOUNDS

by

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PRACTICAL SYNTHESIS OF ALKENYL PHOSPHORUS COMPOUNDS

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ABSTRACT

Current methods to synthesize alkenylphosphorus compounds are not suitable for industrial scale reactions, so this project aimed to develop an efficient, scalable two-step method that could be applied to a variety of readily-available starting materials. To optimize this method, several catalysts, a one-pot process, and various carbonyl substrates were explored. The catalyst $Ti(O\text{-}i\text{-}Pr)_4$ gave the highest yields and enabled aromatic substrates to be utilized, while the one-pot process provided comparable yields with the traditional approach of two-steps with a work-up. Since this method gave good to excellent yields on sterically unhindered and aromatic ketones, future work aims to explore these and various aldehydes substrates, as well as a DOPO substrate to synthesize a vinylphosphonate flame retardant.

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LIST OF ABBREVIATIONS

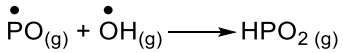
Abbreviation	Full Name
CaH_2	Calcium Hydride
CH_3CN	Acetonitrile
DCM	Dichloromethane
DOPO	9,10-Dihydro-9-Oxa-10-Phosphaphenanthrene-10-Oxide
Equiv.	Equivalent
H_2O	Water
KF on Al_2O_3	Potassium Fluoride on Alumina
$KMnO_4$	Potassium Permanganate
$MgSO_4$	Magnesium Sulfate
N_2	Nitrogen Gas
NaOH	Sodium Hydroxide
P	Phosphorus
rt	Room Temperature
Sat. $NaCl_{(aq)}$	Saturated Sodium Chloride solution
$SOCl_2$	Thionyl Chloride
$Ti(O\text{-}i\text{-}Pr)_4$	Titanium(IV) Isopropoxide

INTRODUCTION

According to the National Fire Protection Association, 1.3 million fires occurred in the U.S. in 2019, leading to 3,700 civilian deaths and over $14 billion in property damage.[1] One way to reduce the risks associated with these fires is to include flame retardants in consumer products, such as building and construction materials, furnishings, transportation vehicles and electronic devices.[2]

Flame retardants work in two main ways: by preventing fires from starting or stopping them from spreading. Depending on their chemical composition, they may do this by bonding to oxygen or other molecules that fuel fire, or by forming a protective layer on a material that would typically be flammable.[2]

The phosphorus atom is unique since it can do both. As a gas, the phosphorus-containing molecules can decompose and react with hydroxyl radicals, removing them from the air and preventing them from fueling the fire. In the solid phase, phosphorus molecules can link together and form a char, which prevents the release of volatile fuel from the burning objects' surface.



Scheme 1: Phosphorus oxide radical reacting in the gas phase to remove the hydroxyl radical.[2]

Often, flame retardants need to be directly incorporated into the solid material they protect. One functionality that can facilitate this is the vinyl group, a particular type of alkene group. The vinyl group's double bond polymerizes with other molecules in the solid matrix, allowing flame retardants with vinyl groups to be directly integrated into the product they protect.

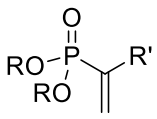


Figure 1: A typical alkenylphosphonate, also called a vinylphosphonate.

This project combines the benefits of phosphorus flame retardants and vinyl polymers by developing an efficient, scalable, and applicable method to synthesize alkenylphosphorus compounds, also known as vinylphosphonates. These compounds feature a phosphorus atom connected to a vinyl group and are produced on an industrial scale, including the molecule in Figure 2 which is a flame retardant in electronic circuit boards.[3]

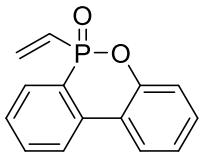
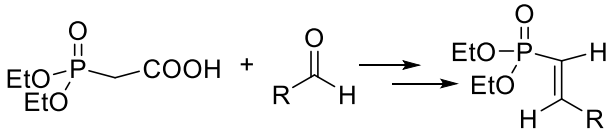


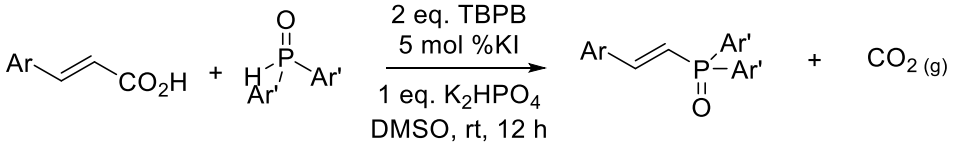
Figure 2: A patented flame retardant; one of the target molecules of this project.

Since these compounds are industrially available, there are already several methods to make them. However, each method has a certain drawback this project hoped to address. First, many of these reactions require multiple steps. For example, Knoevenagel condensation begins with a starting material that is not readily available and requires four steps, one of which is a purification step[4] (Scheme 2). Especially for large-scale industrial reactions, purification can be time-consuming and can require a large volume of solvents, decreasing the time and cost efficiency of Knoevenagel condensation.



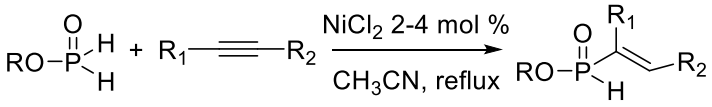
Scheme 2: Utilizing Knoevenagel condensation to synthesize vinylphosphonates.[4]

Secondly, methods like decarboxylation (Schemes 2 and 3) generate $CO_{2(g)}$.[5] On large-scale industrial reactions, this would likely require a reactor capable of withstanding a significant pressure buildup, again decreasing the cost efficiency of the reaction.



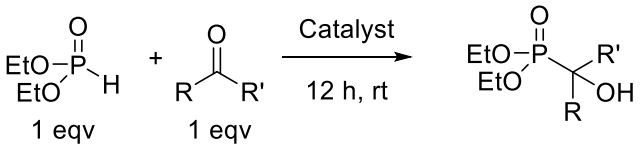
Scheme 3: Decarboxylation producing a vinylphosphonate and $CO_{2\ (g)}$.[5]

Thirdly, some methods only produce a limited number of substituents on the vinyl group. For example, a method developed by Ribière et. al. efficiently synthesizes vinylphosphonates with two substituents on the double bond in the final product [6] (Scheme 4). However, this method utilizes an alkyne starting material, so the product's vinyl substituents are limited to the two substituents on the starting material alkyne. To produce compounds with three substituents, a different method would be required.



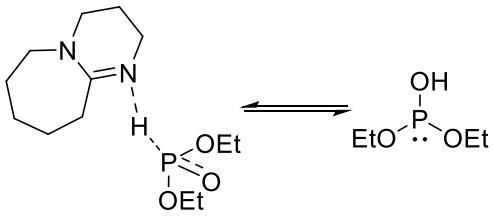
Scheme 4: Efficient method to generate trisubstituted vinylphosphonates.[6]

To address these limitations, this project sought to develop an efficient, scalable method that can be applied to a variety of starting materials. The first reaction step is a Lewis acid or base-catalyzed addition of an *H*-phosphonate to a carbonyl compound, forming a P-C bond in an alcohol intermediate.



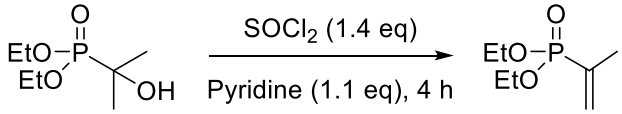
Scheme 5: First step of this method, where R, R' = a hydrocarbon or H.

In the addition step, the catalyst promotes the tautomerization of the five-bonded phosphorus, P(V), to the three-bonded phosphorus, P(III) (Scheme 6). Once in the P(III) form, the P adds to the carbonyl in an Abramov addition reaction.



Scheme 6: P(V) to P(III) tautomerization, assisted by the base DBU.

In the second reaction step, the alcohol group is eliminated with thionyl chloride and pyridine to produce the desired C-C double bond (Scheme 7).



Scheme 7: Second step of this method: elimination of alcohol to form vinyl bond.

To achieve the three main goals of efficiency, scalability, and applicability, this project explored several catalysts, a one-pot process, and a variety of substrates. For efficiency, several Lewis acid and base catalysts were compared to determine which produced the highest percent yield. For scalability, a one-pot process was utilized; it skips the workup or purification of the intermediate

alcohol and instead adds the reagents for the second elimination step directly to the crude reaction mixture. Eliminating this step improves the overall cost and time efficiency of the reaction, increasing its appeal for large scale industrial processes. Finally, a variety of substrates were tested to explore the scope of this reaction.

RESULTS AND DISCUSSION

Table 1: Comparison of Lewis acid and base catalysts on the addition step's percent yields with the acetophenone substrate.

Catalyst	**Result** [(a)]
DBU (1.1 eqv)	Rearrangement
Ultrasound, P(III) Starting Material	0
$Bi(OTf)_3$ (5 mol %)	0
ET_3N (1 eqv)	20
$Ti(O\text{-}i\text{-}Pr)_4$ (5 mol %)	65
KF on Al_2O_3 (3 eqv)	87

(a) Yields obtained by ^{31}P NMR.

Table 2: Comparison of the addition step's percent yields with DBU and Ti(O-*i*-Pr)$_4$ catalysts.

Ketone	**DBU**	**Ti(O-*i*-Pr)$_4$**
Acetone	89	73
Cyclopentanone	83	27
Cyclohexanone	98	54
Acetophenone	Rearrangement	63
Pinacolone	0	---

Table 3: Comparison of DBU and Ti(O-*i*-Pr)$_4$ total percent yields in one-pot process.

Ketone	**DBU**	**Ti(O-i-Pr)$_4$**
Acetone	61	83
Cyclohexanone	12	24
Cyclopentanone	22	---
Acetophenone	---[(a)]	58

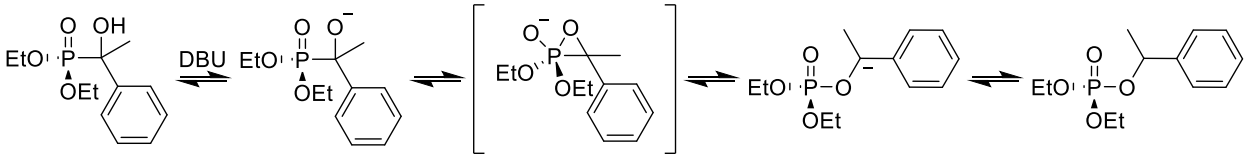
(a) Led to rearranged alcohol intermediate.

Table 4: Comparison of two-step and one-pot processes.

Ketone (Catalyst)	One-Pot	Two-Step w/ Workup
Acetone (DBU)	61	80
Acetone (Ti(O-*i*-Pr)$_4$)	83	---
Acetophenone (Ti(O-*i*-Pr)$_4$)	58	47

Acid vs. Base Catalysts: Efficiency

To optimize the efficiency of the reaction, the addition step was performed with a variety of catalysts, beginning with the classic catalyst for the P(V) to P(III) tautomerization: DBU. With non-aromatic substrates, this catalyst gave excellent yields (Table 2); however, an unexpected result was obtained with an acetophenone substrate. The NMR spectrum revealed the alcohol intermediate had undergone a phospha-Brooks rearrangement promoted by the basic catalyst (Scheme 9).[7]



Scheme 9: Phospha-Brooks rearrangement of intermediate alcohol to a phosphate.[7]

To obtain the correct addition product, several other catalysts, including Lewis acids, were tested on the acetophenone substrate. Two contenders, KF on Al_2O_3 and Ti(O-*i*-Pr)$_4$, gave 87% and 65% yields, respectively. Although the KF on Al_2O_3 gave a higher yield, it was a difficult solid to work with. It not only required an excess, this solid had to be filtered out of the reaction mixture before

the elimination step, preventing a true one-pot process from being utilized. Since the Ti(O-*i*-Pr)$_4$ was a liquid and gave good yields with only a catalytic amount, it was selected as the alternative catalyst for DBU.

When utilizing Ti(O-*i*-Pr)$_4$ in addition reactions with other substrates, the catalyst initially gave lower yields in the addition step (Table 2), most notably with the cyclic compounds. However, it allowed for overall higher yields after both reaction steps with the one-pot process (Table 3). Since it produced higher yields and allowed for aromatic substrates to be utilized, Ti(O-*i*-Pr)$_4$ was chosen as the most efficient catalyst for this method.

One-pot Method: Scalability

More data is needed to establish a strong comparison between the traditional two-step method and the one-pot method; however, preliminary results indicate the one-pot process is a valid alternative. Most notably, it provided comparable yields on acetophenone and acetone substrates (Table 4). One promising result is that switching the catalyst from DBU to Ti(O-*i*-Pr)$_4$ improved the one-pot yield for the acetone substrate from 61% to 83%, which was slightly higher than the two-step method's yield of 80%. While more substrates need to be examined, it appears the Ti(O-*i*-Pr)$_4$ catalyst allows for higher one-pot yields, further increasing the appeal of this simpler, more efficient method.

Reaction Scope: Applicability

This method gave good to excellent yields on a variety of substrates (Table 3). With simple ketones like acetone, it gave excellent yields, and after switching to the Ti(O-*i*-Pr)$_4$ catalyst, it also gave good yields on acetophenone.

With cyclic ketones like cyclohexanone and cyclopentanone, it was not as effective. While the addition steps for both substrates were fair to excellent (Table 2), the elimination step greatly decreased the reactions' yields. One possible explanation for this is the limited number of anti-periplanar H's available for the E2 elimination step. While the acetone substrate has 6 H's available for elimination, the cyclic substrate cyclohexanone only has two (Figure 3).

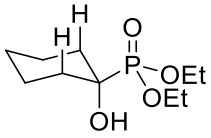
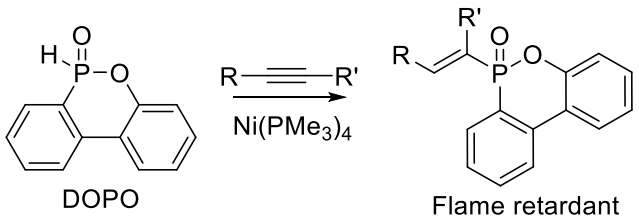


Figure 3: H's available for the anti-periplanar elimination of cyclohexanol.

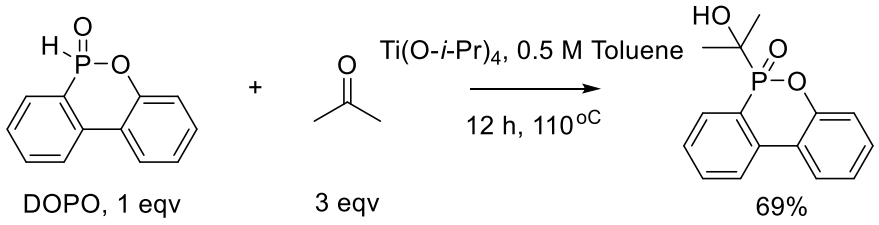
On sterically hindered ketones, such as pinacolone, the bulky tert-butyl group hindered the approach of the P nucleophile, preventing the first addition step from occurring. In the future, other sterically unhindered and aromatic ketones could be targets for this method.

Currently, this method is being tested in the synthesis of a vinylphosphonate that is incorporated into circuit boards as a flame retardant (Figure 2).[3] The current synthetic route (Scheme 10) begins with DOPO, which contains a P-H bond like the *H*-phosphonate starting material of this method. The patented method requires acetylene gas and Ni(0), an air-sensitive metal that is rarely utilized in large quantities, making the current method difficult to conduct on an industrial scale. The method presented in this work avoids flammable metals and utilizes readily-available starting materials, so it offers a valuable alternative route to produce this industrially-relevant compound.



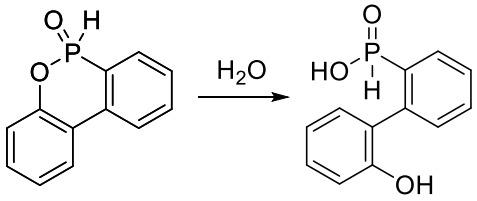
Scheme 10: Current method to synthesize the target vinylphosphonate flame retardant.[3]

Preliminary results have shown the Ti(O-*i*-Pr)$_4$ catalyzed addition of DOPO to acetone is successful, with an unoptimized yield of 69% (Scheme 11).



Scheme 11: Addition of DOPO to acetone in the first step to synthesize a flame retardant.

However, the elimination step has so far been unsuccessful, likely due to the presence of a phosphorus-containing impurity in the starting material. This impurity is the result of water contaminating the DOPO starting material and reacting to produce a compound with a phenol group (Scheme 12). The phenol group seems to react with the $SOCl_2$ and pyridine, preventing the desired formation of the vinyl group. Future work will focus on isolating the DOPO starting material via a basic workup, then optimizing both reaction steps to obtain the industrially-relevant flame retardant.



Scheme 12: Hydrolysis of DOPO starting material to produce phenol impurity.

CONCLUSION AND FUTURE WORK

In addition to the completion of the flame retardant synthetic route, one area of future exploration is the use of aldehyde substrates. In theory, the aldehyde's carbonyl C is more electrophilic than the ketone's carbonyl C, so the aldehyde should be more reactive. So far, one aldehyde, isovaleraldehyde, has been tested and gave a total one-pot yield of 63%, which suggests other aldehydes may also be candidates for this method.

By exploring several acid and base catalysts, testing a one-pot method, and employing various ketone substrates, this project has produced a simple, efficient method that can be applied to a variety of starting materials and may have a practical use in the flame retardant industry.

EXPERIMENTAL PROCEDURE

General Chemistry:

^{31}P NMR and ^{1}H spectra were recorded on a 400 MHz Bruker Avance spectrometer. Chemical shifts for ^{1}H NMR spectra (in parts per million) were measured relative to the internal standard tetramethyl silane (Me_4Si, $\delta = 0.00$ ppm). Column chromatography experiments were carried out on Silica Gel Premium Rf grade (40-63 μm). Ethyl acetate/hexanes mixtures were utilized as the eluent for chromatographic purifications. TLC plates were visualized by UV or immersion in potassium permanganate (3g $KMnO_4$, 5 mL 5% aq. NaOH and 300 mL H_2O) followed by heating.

Reagents and solvents:

All starting materials were purchased from commercial sources and used as received. The solvents were distilled under N_2 and dried according to standard procedures (CH_3CN, toluene, and DCM from CaH_2).

First Step- Addition with Ti(O-i-Pr)$_4$ catalyst and non-DOPO substrates:

A 1 mL round bottom flask containing diethylphosphite (1 equiv, 0.26 mL, 2.0 mmol) was flushed with N_2. For acetone, cyclohexanone, and cyclopentanone, 3 equiv (6 mmol) were used; for acetophenone and isovaleraldehyde 1 equiv (2.0 mmol) was added. Ti(O-*i*-Pr)$_4$ (5 mol %, 0.03 mL, 0.1 mmol) was added with a micropipette. The reaction was left to stir at room temperature for 12-24 hours.

For the non-one pot process, the following substrate's addition product was worked up as follows.

Acetone, 20 mmol scale-The crude reaction mixture was dissolved in 50 mL DCM; 20 mL sat. $NaCl_{(aq)}$ were added. The aqueous layer was extracted with 5 x 10 mL DCM. The organic layers were combined, dried with $MgSO_4$, concentrated, and left under vacuum for 3 days. The isolated product was purified with column chromatography. ^{31}P NMR (400 MHz, $CDCl_3$): δ = 23.97 (s, 87%), 23.17 (s, 10%).

First Step with DBU catalyst on non-DOPO substrates:

Conducted as above except the ketone was dissolved in 4.00 mL acetonitrile (0.5M), and Ti(O-*i*-Pr)$_4$ was replaced with DBU (1.1 equiv, 0.33 mL, 2.2 mmol).

First Step- DOPO Addition:

DOPO (1 equiv, 432 mg, 2.0 mmol) was added to a sealed tube that was flushed with N_2. Toluene (distilled, 4.00 mL) was added, then acetone (3 equiv, 0.44 mL, 6.0 mmol) and Ti(O-*i*-Pr)$_4$ (5 mol %, 0.03 mL, 0.10 mmol) were added. The mixture was stirred and heated at 120$^{\circ C}$ overnight. ^{31}P NMR (400 MHz, $CDCl_3$): δ = 34.75 ppm (sextet, 69%, product); 13.39 ppm (dd, 20%, hydrolyzed DOPO).

Second Step- Elimination:

The addition product (crude, unless worked up after the addition step) was transferred to a 10 mL round bottom flask with 4.00 mL distilled toluene. Pyridine (1.1 equiv, 0.18 mL, 2.2 mmol) was added while stirring, then $SOCl_2$ (1.4 equiv, 0.20 mL, 2.8 mmol) was added while stirring. The reaction was left to stir at rt for 4 hrs.

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