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In Pursuit of a Stable Luminescent Radical: Investigating an Olefin Synthesis via the Horner-Wadsworth-Emmons Reaction

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In Pursuit of a Stable Luminescent Radical: Investigating an Olefin Synthesis via the Horner- Wadsworth-Emmons Reaction

By
Kelly X. Vences

A Thesis Submitted in Candidacy for Honors in Independent Study from
Lawrence University, May 2021.

I hereby reaffirm the Lawrence University Honor Code.

Kelly X. Vences

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Acknowledgements

I would like to express my gratitude and appreciation for my research advisor Dr. Graham Sazama, for giving me the opportunity to take on this project. I have had so much fun learning the fascinating underlying chemical concepts that drive our scientific research.

I would also like to thank Professor Stefan Debbert and Professor Allison Fleshman for instilling in me their knowledge and passion for their field of research.

I thank Daniel Martin for creating a productive lab environment and helping with all my technical difficulties.

Abstract

We investigate the synthesis of allyl radical compounds, such as C. F. Koelsch's free radical bis(diphenylene)-9'-phenylallyl (BDPA). BDPA is a persistent organic radical with magnetization properties. BDPA does not fluoresce, but we believe the substitution of a fluorene group with the chromophore 1-azaxanthone will induce luminescent properties and create a BDPA[•] derivative bis(diphenylene)-9'-azaxanthylene phenylallyl (BAxPA[•]). A convergent synthetic path was conducted in the development of BAxPA. The synthesis of 1-azaxanthone via a Friedel crafts reaction and a subsequent condensation produced the chromophore. The BDPA framework was created via varying Pudovik reactions that gave precursor molecules that will be used for the Horner-Wadsworth-Emmons reaction which combines azaxanthone with the BDPA framework. Several synthetic issues are explored in this investigation and a proposal for a new HWE route ensues. NMR and EPR spectroscopy are used to identify and characterize the compounds.

Introduction

Persistent Organic Radicals

Radicals are difficult to stabilize because of their open-shell valency, but recently developed radical compounds have materials chemists excited about their potential to link electron spin and its associated magnetic phenomena with other device-relevant properties, including recent work on luminescence.¹⁻⁶ Coupling these magnetic spin properties with luminescence can be useful for applications and devices such as organic light-emitting diodes (OLEDs), batteries, and organic semiconductors.⁷⁻¹¹ In this work, we compared two main radical frameworks, one with precedent for luminescence, and the other without. In our aim to develop open-shell luminescent compounds, we propose a new design for persistent organic radicals based on Koelsch's allyl radical bis(diphenylene)-9'-phenylallyl (BDPA). We attempt to incorporate a chromophore moiety known as 1-azaxanthone into the BDPA framework via a Horner-Wadsworth-Emmons reaction. It is our motivation to induce luminescent properties in a BDPA radical derivative, called bis(diphenylene)-9'-azaxanthylene phenylallyl (BAxPA).

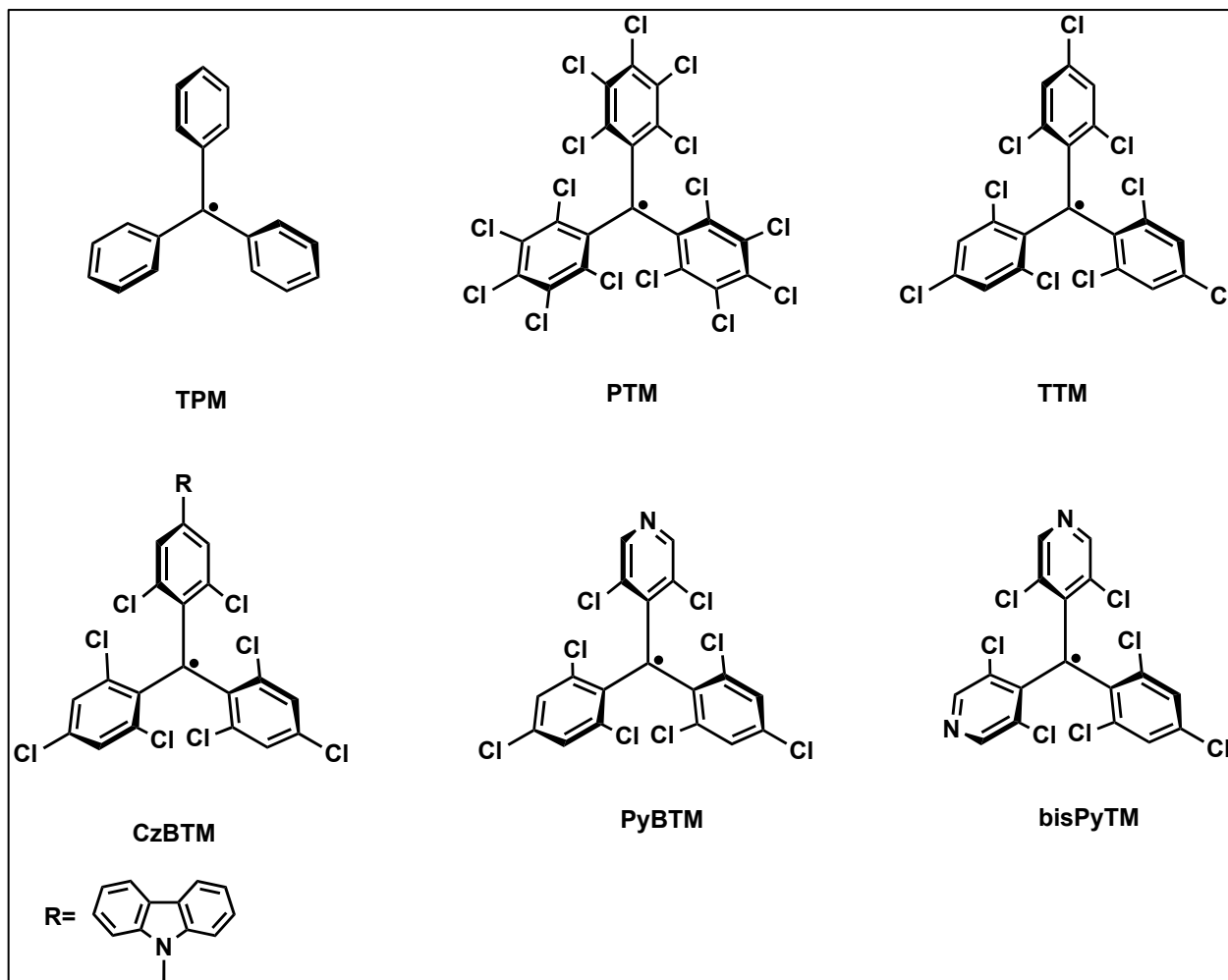
Triarylmethyl Radicals

Radicals are compounds with an unpaired electron that possesses either a $+1/2$ spin or a $-1/2$ spin orientation.¹² There are only two allowed orientations of a single electron called a doublet state, D. This state corresponds to the open shell of radical that possesses an unpaired electron.¹²

In 1900, Moses Gomberg published his discovery of the first known organic triphenylmethyl (TPM) radical (**Chart 1**).¹³ Gomberg reported the synthesis of a trivalent compound, a three-coordinate carbon center with an unpaired electron, that exhibited semi-stable properties. With the emergence of Gomberg's radical, several derivative triarylmethyl (TAM) radicals have been

produced.¹⁴ One such example of a persistent TAM radical comes from Manuel Ballester's group, the perchlorotriphenylmethyl radical (PTM) reported in 1971.¹⁵

Chart 1. Triarylmethyl Class of Free Radicals.



Compared to TPM, Ballester et al. found that PTM had a greater stability with a lifetime of 4-16 days at room temperature, whereas TPM is stable only in solution in an inert environment under reduced pressure. Ballester et al. found that steric shielding of the tetravalent alpha carbon is the predominant factor attributed to its high stability. The sp^2 carbon is crowded by polychlorinated

phenyl rings that possess high shielding abilities. Additionally, the chlorine shield of the atoms in the ortho positions hinder potential reactivity between the sp^2 carbon and other reactive species. Spin delocalization onto the phenyl rings is limited by the twisted propeller-like conformation, and as such, resonance is a small factor in the stability of the radical. Interest in the photochemistry of PTM by Marye Anne Fox et al. led to the exploration of its excited doublet state. Fox et al. reported an emission maximum at 605 nm with a fluorescence quantum yield of 0.015 ± 0.005 .¹⁶ Whilst Ballester et al. paved the way for the synthesis of several polychlorinated PTM based radicals, Fox ignited an interest in the photoluminescent properties of TAM based radicals.

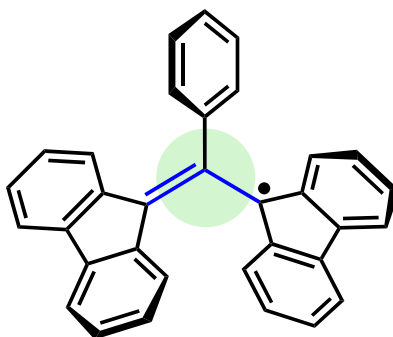
In 1987 Veciano et al. published their work on the synthesis and isolation of several PTM radical derivatives that had varying chlorine atoms on the phenyl rings. Veciano et al. developed tris(2,4,6-trichlorophenyl)methyl (TTM, Scheme 1), marking a new category of TAM radicals since the PTM series.¹⁷ An assessment on the influence meta and ortho chlorines have on the twist angles of the phenyl rings and stability of the radicals was conducted. X-ray crystallography measurements corroborated Ballester's groups findings on the effect ortho positioned chlorines have on the propeller-shape structure of the radical. The absence of meta-positioned chlorines does not influence the stability of the molecule. Thus, the TTM radical derivatives show increased stability in the solid state or in solution.

Several TTM based radicals were produced by the Julia group with varying functional groups replacing a para-chlorine on a phenyl ring.¹⁸⁻²¹ Julia and coworkers synthesized the radical (4-N-carbazolyl-2,6-dichlorophenyl)bis(2,4,6-trichlorophenyl)methyl (CzBTM) derived from the TTM skeleton where carbazole replaced a p-chlorine.²² Most notably, the addition of the carbazole moiety produced novel photoluminescent properties in its excited doublet state.⁴ Carbazole fluoresces at ~340 nm and has electronic properties prompted by the nitrogen atom making it a

good chromophore.²² Julia et al. proposed the non-bonding electrons on the nitrogen exhibit properties similar to π - π^* transitions.²² Carbazole-containing compounds are known to exhibit high charge carrier mobility and exhibit high photochemical stability.²³⁻²⁵ These properties are attributed to diminished electron withdrawing capacity of nitrogen due to donation of its lone pair due to a mesomeric effect.²³ In this vein, the application of the carbazole adduct to the TTM skeleton is a mix of the redox and paramagnetic character of TTM with the photoluminescence properties of carbazole. Julia et al. found that the CzBTM radical has an emission maximum at 628 nm and a fluorescence quantum yield of 0.53 in cyclohexane.²² To my knowledge, CzBTM was the first example of a fluorescent radical with stable properties.

Recent development of a novel luminescent radical, (3,5-Dichloro-4-pyridyl)-bis(2,4,6-trichlorophenyl) methyl (PyBTM), in 2014 by Nishihara et al elucidate further methods for engendering fluorescence into the TTM framework.²⁶ The substitution of a phenyl ring with a pyridine ring moiety was the first known instance of this inclusion to the TTM framework. The calculated lifetime of the stable luminescent radical is reported as 6.4 ± 0.2 ns with a fluorescence quantum yield of 0.81 in EPA (diethyl ether:isopentane:ethanol 5:5:2 v/v).²⁶ Nishihara et al. found that the addition of pyridyl rings directly corresponds to the lowering of the energy levels of the frontier orbitals, causing the radical's higher stability.²⁶ The lifetime and photostability is 115 times better for PyBTM than the original TTM skeleton (**Chart 1**).²⁶

Nishihara et al.'s work has fueled the synthesis of new luminescent radical compounds, expanding the roster of known radical emitters.^{27,28} However, all the known luminescent radical compounds are based on the TTM skeleton which limits the scope of our understanding of the photophysics of compounds with a doublet ground state.



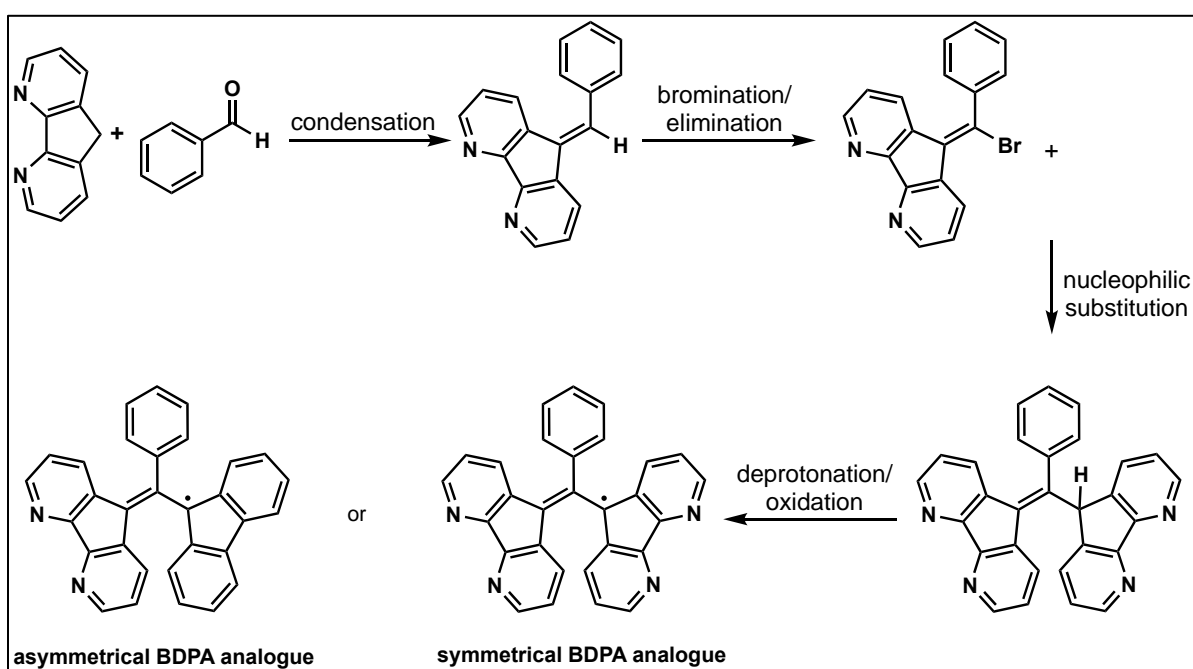
BDPA

Figure 1. Koelsch's radical bis(diphenylene)-9'-phenylallyl (BDPA) is a stable free radical. Highlighted in green is the allyl radical pattern: C-C double bond and a tetravalent carbon.

In order to understand the photophysical properties of radical compounds more broadly than in just a single radical framework, we seek to investigate radicals based on the allyl radical framework established by Koelsch's free radical, bis(diphenylene)-9'-phenylallyl (BDPA). In 1957 Koelsch created a highly air-stable compound that boasts greater oxygen stability compared to TTM and PTM radicals, which are very stable under anaerobic conditions.²⁹ Azuma et al. have shown BDPA is a monomeric species in the solid state.⁵ The allyl radical framework has resonance delocalization throughout the molecule contributing to a higher stability. Unlike the TTM series which only contains substituted benzyl rings, BDPA encloses the tetravalent carbons with symmetric propeller-like fluorene adducts that are bulky and sterically hindered (**Figure 1**).

Currently, BDPA radical analogues are generally created via condensation pathways. Plater et al. developed several 4,5-diazafluorene derivatives of BDPA using Neugebauers route.³⁰ The aldol condensation of 4,5-diazafluorene with benzaldehyde, a bromination, and an HBr elimination produce Michael acceptors.³¹ Next, fluorene or 4,5-diazafluorene reacts with the Michael acceptor

and the BDPA radical precursors are made (**Scheme 1**).³¹ The subsequent oxidation of the radical precursors produce symmetrical or asymmetrical free radical analogues of BDPA. The four nitrogen atoms are more likely to react with proton sources and oxidize rapidly. The symmetrical radicals (**Scheme 1**) are less stable than BDPA and are a more chemically reactive species. Plater's BDPA analogues are not fluorescent, but an asymmetric BDPA radical framework has been synthesized and shows a greater stability than the symmetric BDPA radical analogues.³¹

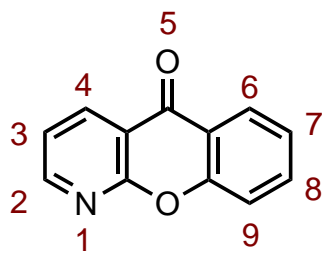


Scheme 1. General Condensation Pathway for BDPA Analogues

Swager, Wang et al. developed a different synthetic route for BDPA analogues.³² They designed phosphonate synthons, products of Pudovik reactions, that are electron rich substrates useful for organic synthesis.³² This method expanded the scope of BDPA analogues by providing phosphonate scaffolds that easily react with fluorenone via a Horner-Wadsworth-Emmons (HWE)

reaction. Hence, BDPA analogues were produced in quantitative yields. We utilized this synthetic route which promotes a new approach to asymmetric BDPA derivative compounds.

The chromophore



1-Azaxanthone

Figure 2. The chromophore 1-azaxanthone. Naming begins at the nitrogen in the one-position.

We believe the addition of a chromophore into the Koelsch radical framework is essential in producing fluorescence emission. Our synthetic mechanism requires a substitution of a fluorene moiety with a fluorophore that disperses the electronic charge throughout the radical. We hypothesize that a Horner-Wadsworth-Emmons reaction opens a pathway to radical precursors containing a chromophore in place of one of the fluorenes. We can then study the double-state properties of the radical and quantify the fluorescence emission and lifetime.

In our aim to create a luminescent radical based on the allyl radical framework, we need to find a chromophore that is synthetically amenable and likely to engender photoluminescent properties. Azaxanthone is an aromatic ketone whose photophysical properties were investigated by J.C. Scaiano in different micellar environments and aqueous solutions.^{33,34} Scaiano et al. observed phosphorescence emission of azaxanthone in the triplet state, upon laser excitation.³⁵⁻³⁷ Fluorescence emission at 415 nm was observed in water, but not acetonitrile, in the singlet excited

state at room temperature.³⁵ Scaiano found that solvent-solute interactions between azaxanthone and the solvent do not account for the observed fluorescence.³⁵ Hydrogen bonding between the nitrogen atom on azaxanthone and water do not play a key role henceforth D₂O was used in further experiments which further reveal fluorescence emission is not produced from the solvent environment.³⁵ Furthermore, a decrease in fluorescence emission was measured under strongly acidic conditions.³⁵ When azaxanthone is added to 1N H₂SO₄, the fluorescence intensity reduced by 50%.³⁵ Thus, the emission is assigned to the pyridinium cation of azaxanthone.

Scaiano et al. studied the photophysical properties of azaxanthone in its singlet and triplet states.³⁵⁻³⁷ Moreover, Scaiano's experiments imply there is a reduction in intersystem crossing between the singlet and triplet states prompting weak fluorescence emission. Majima et al. conducted transient absorption and emission studies on the short-lived azaxanthone ketyl radical, determining the quantum yield and lifetime of the azaxanthone ketyl radical doublet state.³⁸

Majima et al. found that the azaxanthone ketyl radical fluoresces at 645 nm which corresponds to a D₁-D₀ transition.³⁸ A second laser pulse was applied to the ketyl radical (355 nm, 1 mJ pulse⁻¹) which resulted in fluorescence at the UV range of 460 nm (Figure 3).³⁸ This transition corresponds to an excitation between the D₂-D₀ states. The fluorescence quantum yields for the D₁-D₀ transition is 0.0008 ± 0.0002 and 0.05 ± 0.02 for the D₂-D₀ transition.³⁸ The lifetime of the ketyl radical in a D₁-D₀ transition was 0.4 ns and 1.0 ns in the D₂-D₀ transition.³⁸

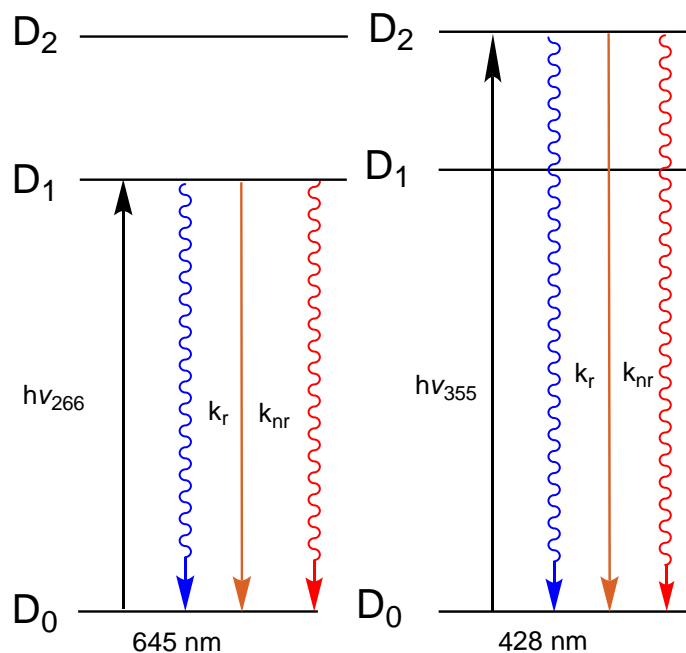
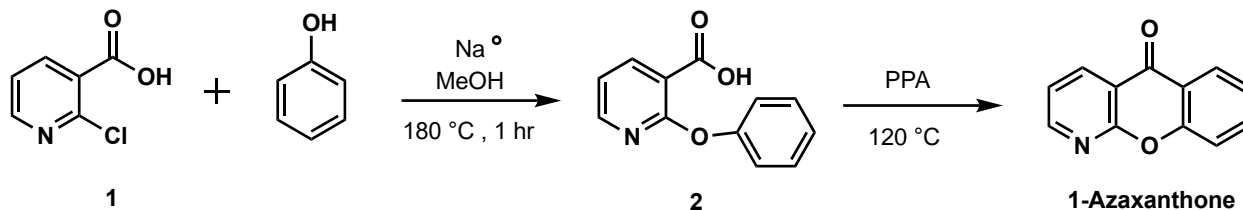


Figure 3. Energy-level diagrams of $\text{AXH}\cdot$ (D1, left) and the D2 transition (right).

The anomalous fluorescence of the ketyl radical is attributed to the pyridine ring in azaxanthone.³⁸ Accordingly, the nitrogen atom holds an electronegative charge that leaves the ketone CO-bond exposed to nucleophilic attack.³⁸ This leaves a heightened reactivity at the alpha-carbon which can be used in a Horner-Wadsworth-Emmons reaction. We are synthesizing Koelsch's radical via a Pudovik reaction between phosphonate and benzaldehyde, which can then react with azaxanthone.

Results and Discussion

Chromophore Synthon- 1-azaxanthone:



Scheme 2. Synthetic Strategy of 1-Azaxanthone.

As outlined in **Scheme 2**, a Friedel-Crafts reaction was conducted to make compound **2**, the precursor synthon to azaxanthone. This reaction produced a 56% yield of a dark yellow powder. Compound **2** underwent a condensation that produced the desired chromophore, 1-azaxanthone, at 20% yield. (**Figure 4**). The extraction of the crude material from a PPA and water mixture results in a loss of product, especially considering the high solubility of azaxanthone in water.



Figure 4. Recrystallized azaxanthone from ethanol produced spidery yellow-white needles.

NMR spectroscopy of compound **2** showed 8 peaks corresponding to the frequencies of the aromatic hydrogens (**Scheme 2**). The peak corresponding to the hydroxy group was too broad and potentially out of the range of the spectrum of our NMR instrument. The GC/MS chromatogram shows the presence of the hydroxy group and provides the structure of compound **2**. The mass ion of compound **2** was detected at 13.508 minutes at 214 m/z (**Figure 5**). GC/MS library search also showed the abundance of compound **2** (**Figure 6**).

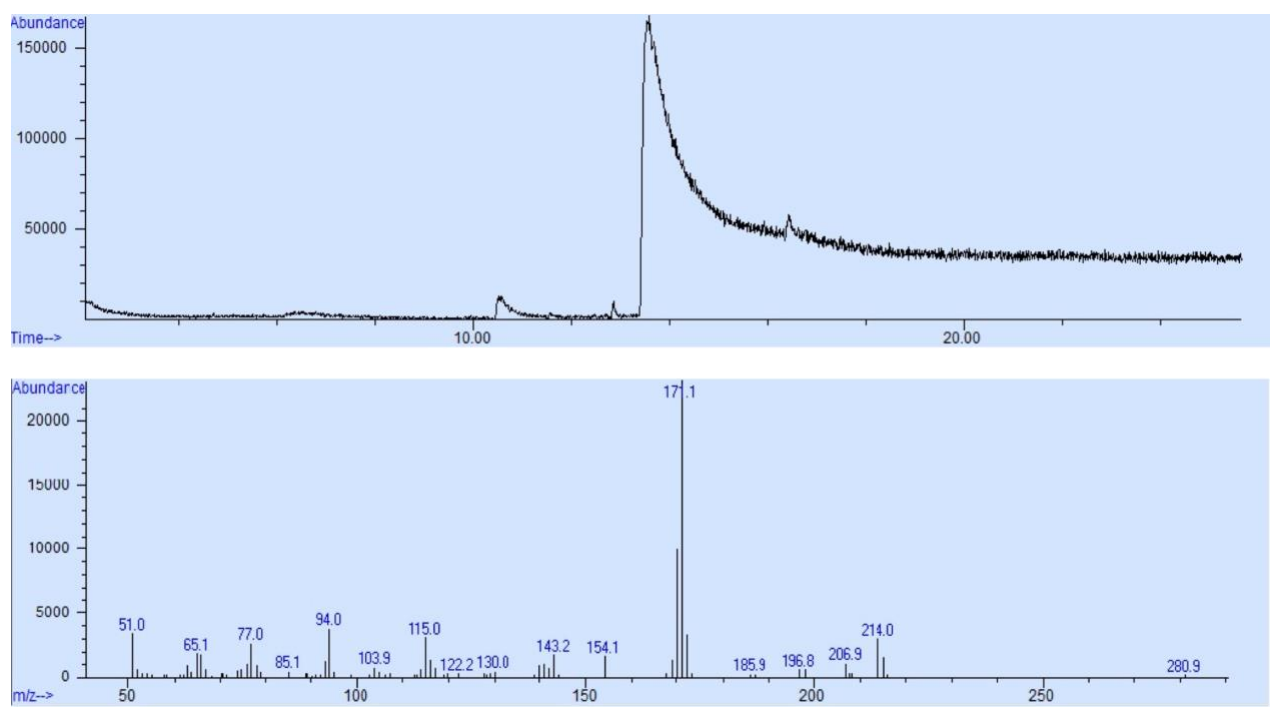


Figure 5. GC/MS chromatogram of 2-phenoxy nicotinic acid (compound **2** in **Scheme 2**).

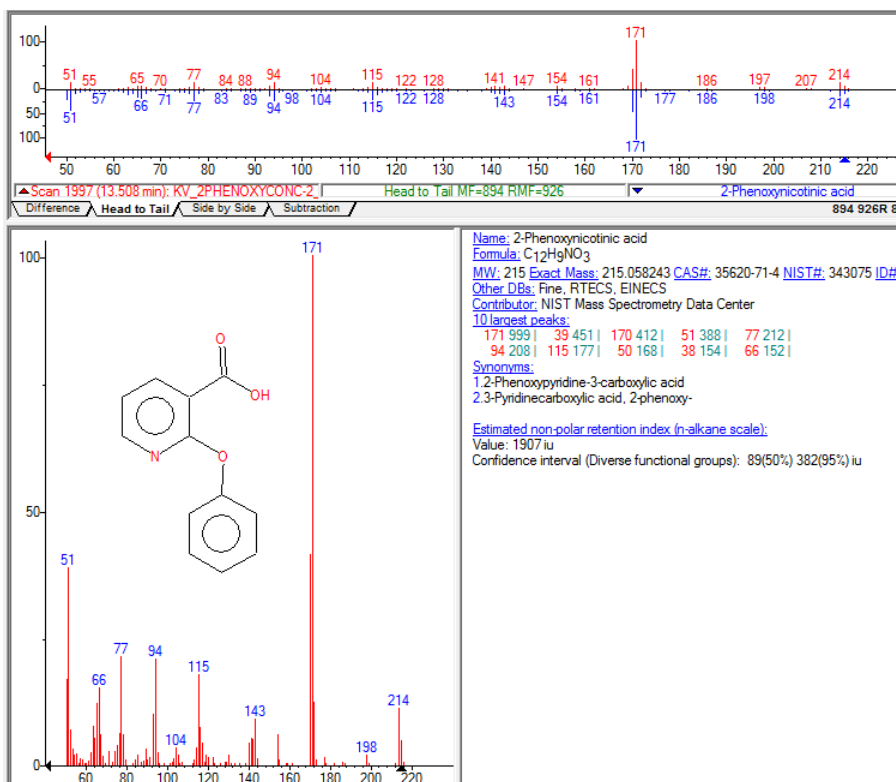


Figure 6. A library search by mass ion shows the chemical structure of compound **2**.

Azaxanthone was characterized via ^1H and ^{13}C NMR spectroscopy. Herein, we report 1-azaxanthone spectra with coupling values and integral values. To our knowledge, there have been no reported spectra in the literature. There are a total of seven hydrogens in the compound and we find seven resonating frequencies (**Figure 7, 8**). Scaiano et al. pioneered the naming system for azaxanthone, and chemical manufacturers alike label the nitrogen atom next to the oxygen in the ring at the 1-position (**Figure 2**).^{35–37} The ^1H NMR spectrum of 1-azaxanthone are shown in figures **7** and **8**. ^1H NMR (400 MHz, CDCl_3) ppm: $\delta = 7.42\text{--}7.47$ ppm (ddd, $J = 10.96, 7.6, 5.57$ Hz, 2H), $\delta = 7.65$ ppm (d, $J = 8.61, 1.18$ Hz, 1H), $\delta = 7.80$ ppm (td, $J = 7.04, 1.96$ Hz, 1H), $\delta = 8.33$ ppm (d, $J = 8.2, 2.0$ Hz, 1H), $\delta = 8.73$ ppm (d, $J = 7.63, 2.15$ Hz, 1H), $\delta = 8.76$ ppm (d, $J =$

4.5, 2.35 Hz, 1H). The chromatogram of 1-azaxanthone indicates the mass ion of 197.0 m.z as the molecular weight (**Figure 9**).

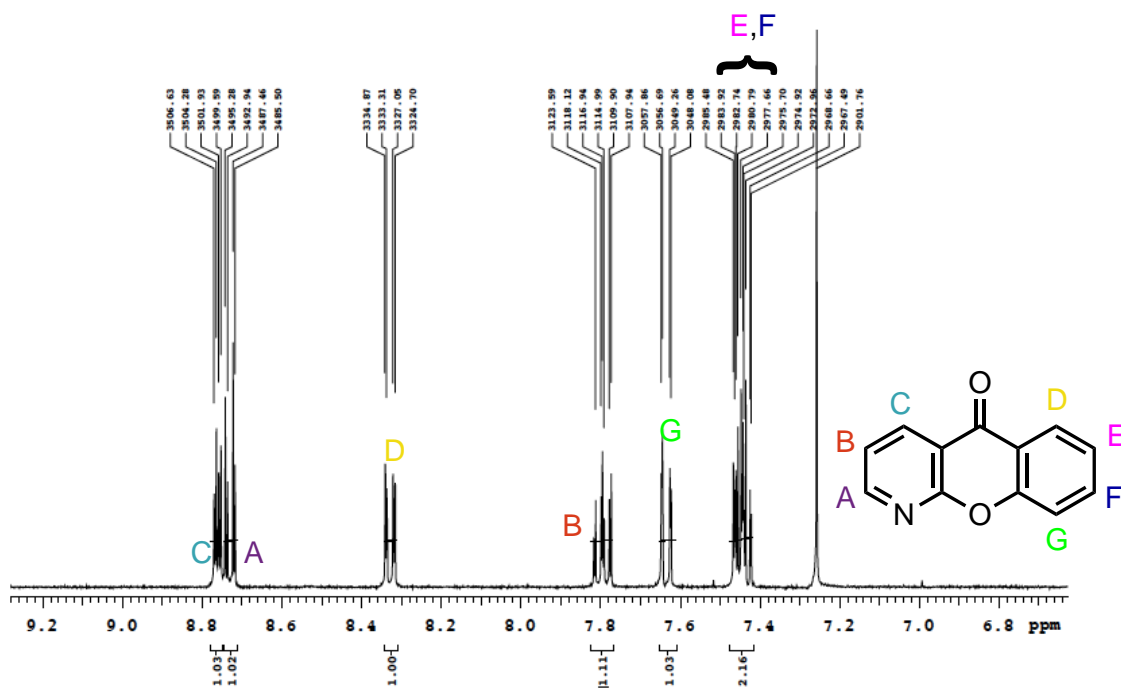


Figure 7. ¹H NMR spectrum of 1-azaxanthone in CDCl₃ showing solvent residue at 7.26 ppm.

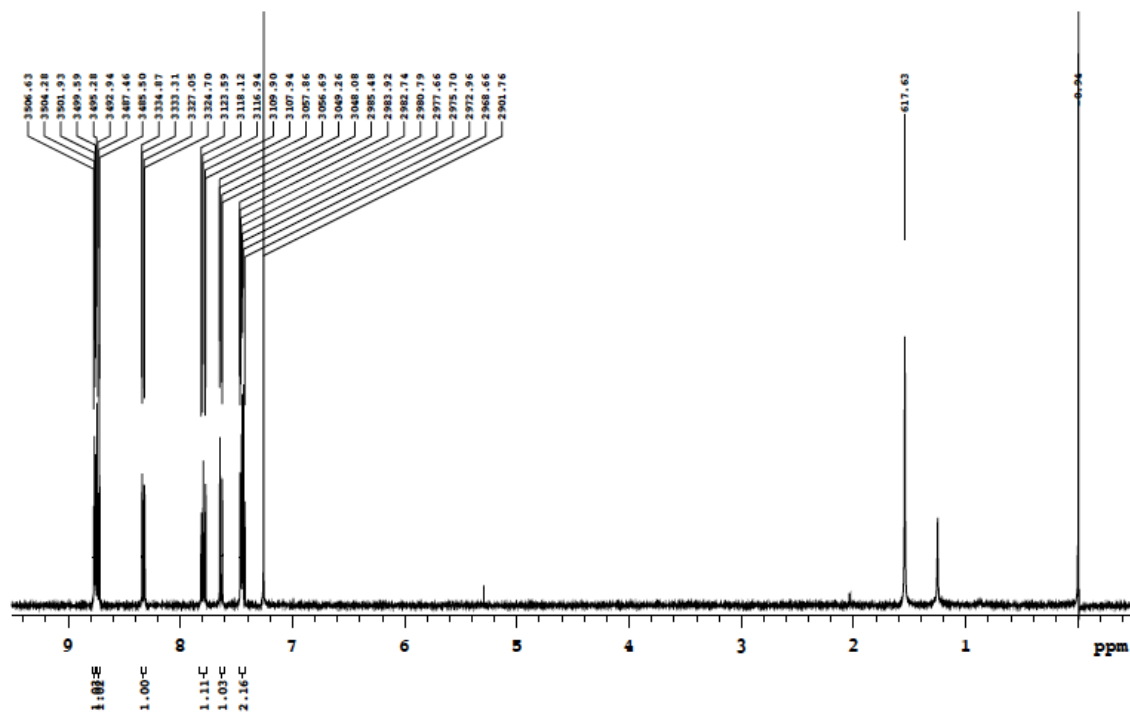


Figure 8. Full ^1H NMR spectrum of 1-azaxanthone in CDCl_3 . Peaks at 1.26 ppm and 1.56 ppm are ethanol and water impurities respectively.

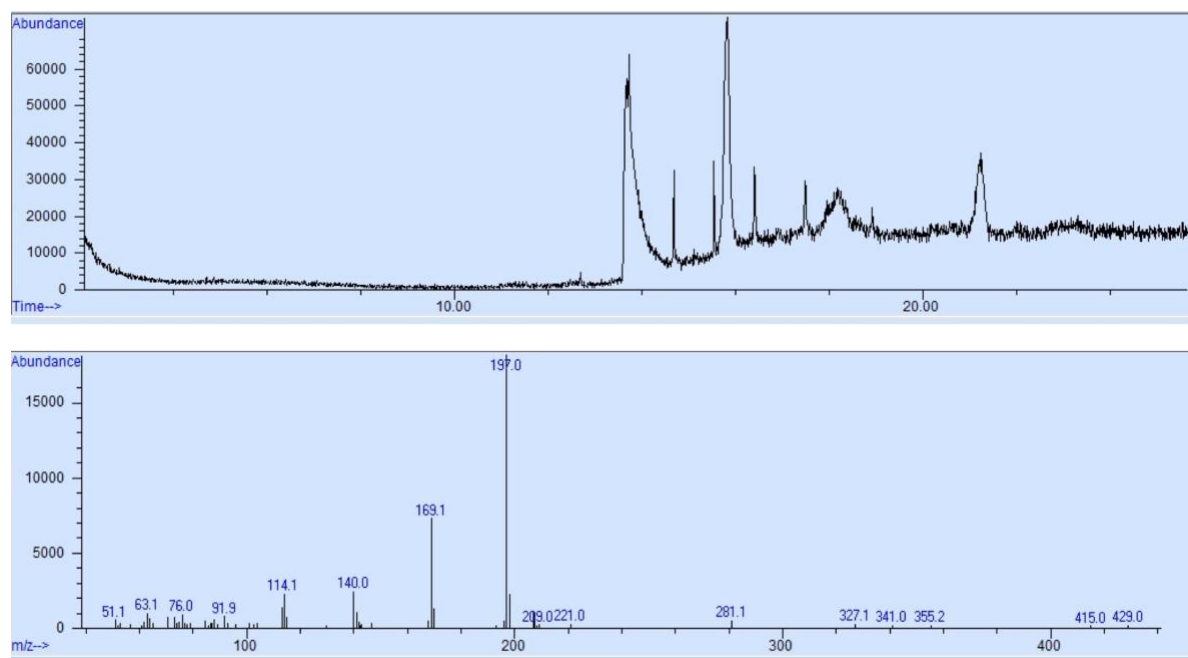


Figure 9. GC-MS spectra shows the molecular weight and abundance of 1-azaxanthone.

The optical properties of azaxanthone were investigated via UV-Vis analysis. Scaiano and Martinez reported azaxanthone's absorption maxima at 282 and 329 nm in water and 284 and 335 nm in acetonitrile.³⁵ We report absorption maxima at 283 and 332 nm in CH₂Cl₂ as **Figure 7** illustrates. The presence of the ketone would generally correspond to an $n-\pi^*$ transition such as the absorption maxima at 233 nm. However, the aromaticity of azaxanthone delocalizes the pi electrons and the promotion of an electron from its highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) in azaxanthone corresponds to a $\pi-\pi^*$ transition. We want our chromophore to exhibit this property like carbazole, which has high stability and photoluminescent properties.

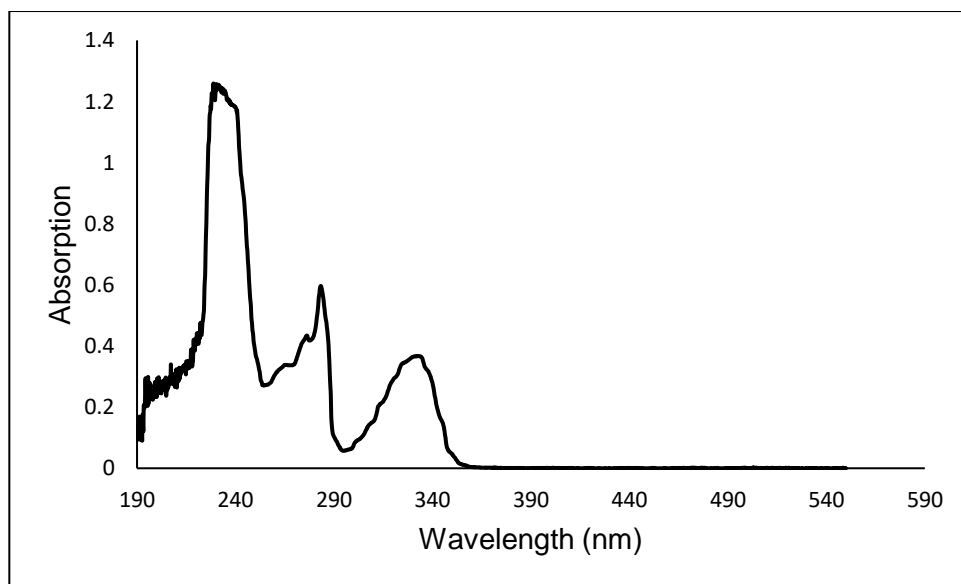
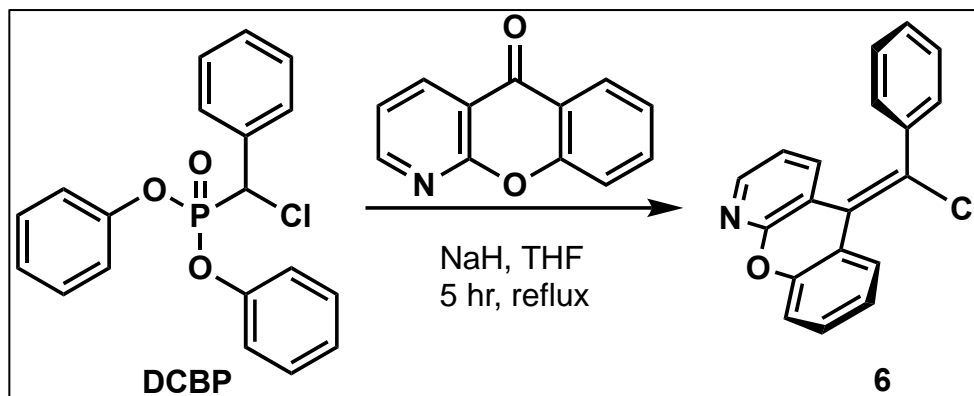


Figure 11. Absorption spectrum of 1-azaxanthone in DCM at room temperature, at a range of 190 nm to 500 nm.

Pudovik Synthons:

Scheme 3. An unsuccessful Horner-Wadsworth-Emmons reaction using the commercially available substrate diphenyl alpha-Chlorobenzylphosphonate.



Once we successfully produced the chromophore, the next synthetic goal was to incorporate it into the BDPA framework. Using a commercially available substrate, we conducted an HWE olefination reaction (**Scheme 2**). We screened several strong bases, such as NaH, KOH with 18-crown-6, and *t*BuOK and found the reaction gave no quantifiable amounts of the desired product (**Table 1**). We posited that the phenoxy groups on the phosphonate are too bulky and steric hindrance prevents the ylide from forming.

A different phosphonate substrate was identified as a better precursor for the HWE reaction. Phosphonate **5**, features ethyl substitution instead of the bulkier phenyl rings, was prepared according to literature methods (**Scheme 3**), and NMR and GC/MS spectroscopy were used to characterize the desired product.³² In contrast with the unsuccessful diphenyl phosphonate ester, the reduced steric bulk of the ethoxy groups of **5** proved sufficiently unhindered to prepare compound **6** (**Scheme 3**).

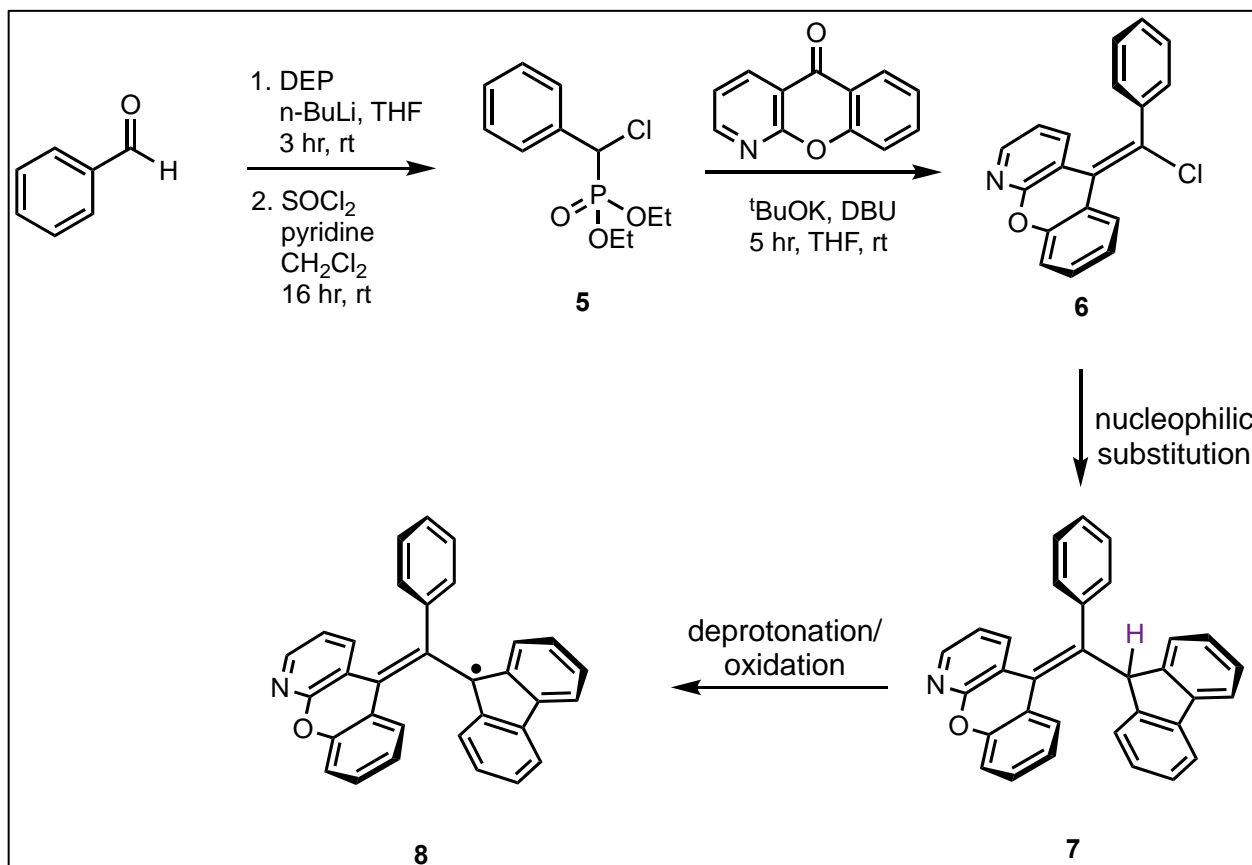
Table 1. Base Screening Reaction Conditions

Entry	Base	Molar Ratio ^a	Solvent	Temp °C	Time
1	t-BuOK	1.0:1.0:1.0	THF	rt	5 hrs
2	t-BuOK	1.0:1.0:1.5	THF	reflux	5 hrs
3	t-BuOK	1.0:1.0:2.0	THF	reflux	10 hrs
4	t-BuOK	1.0:1.0:3.0	THF	reflux	10 hrs
5	t-BuOK	1.0:1.2:5.0	THF	reflux	10 hrs
6	NaH	1.0:1.0:1.0	THF	rt	5 hrs
7	NaH	1.0:1.0:1.2	THF	reflux	5 hrs
8	NaH	1.0:1.0:1.5	THF	reflux	5 hrs
9	NaH	1.0:1.0:3.0	THF	reflux	5 hrs
10	NaH	1.0:1.0:3.5	THF	reflux	10 hrs
11	NaH	1.0:1.0:3.5	THF	reflux	10 hrs
12	NaH	1.0:1.0:5.0	THF	reflux	5 hrs
13	KOH	1.0:1.0:2.0	THF	rt	5 hrs
14	KOH	1.0:1.0:2.5	THF	reflux	10 hrs
15	KOH	1.0:1.0:3.0	THF	reflux	10 hrs

^aMolar ratio of **DCBP/1-azaxanthone**/base.

Scheme 4. Synthetic Strategy for BxPA via a HWE Reaction Using Pudovik Precursor

Synthons



To test the viability of compound **6** for formation of the BxPA radical, crude product was subjected to addition of the fluorene group. The addition of fluorene produced a deep purple color (**Figure 8**) and the closed-shell BxPA molecule was created (compound **7** in Scheme 4). A deprotonation and oxidation followed to produce radical compound **8**.

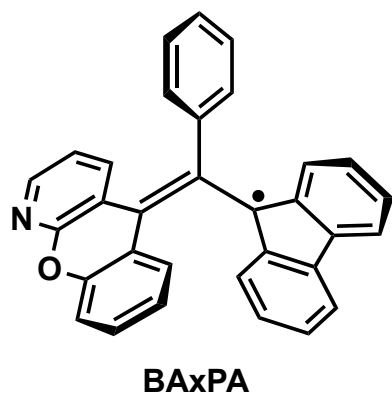


Figure 12. Chemical structure of BAxPA (left) and BAxPA in solution (right).

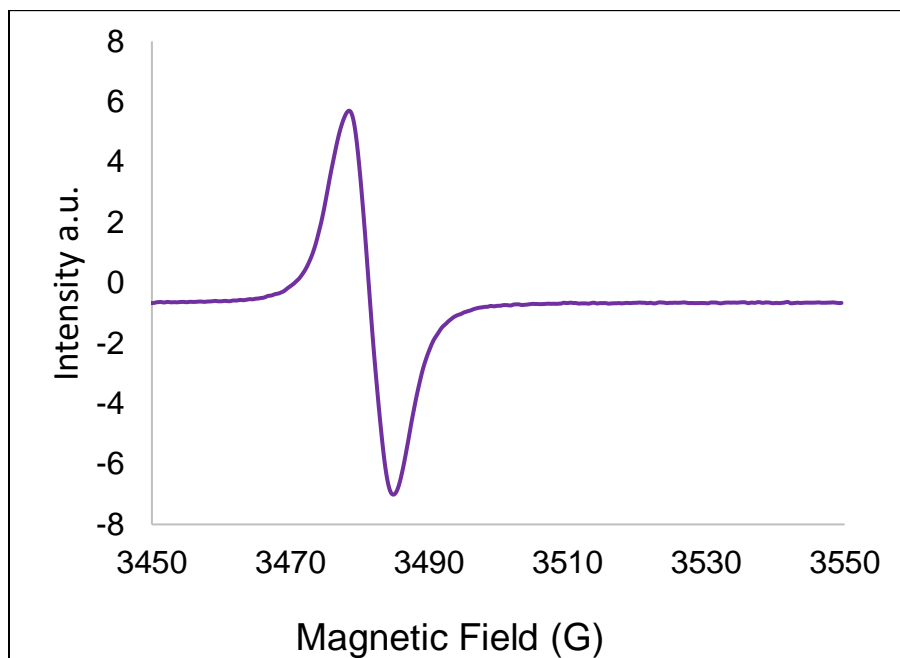


Figure 13. An EPR spectrum of BAxPA* in toluene at room temperature.

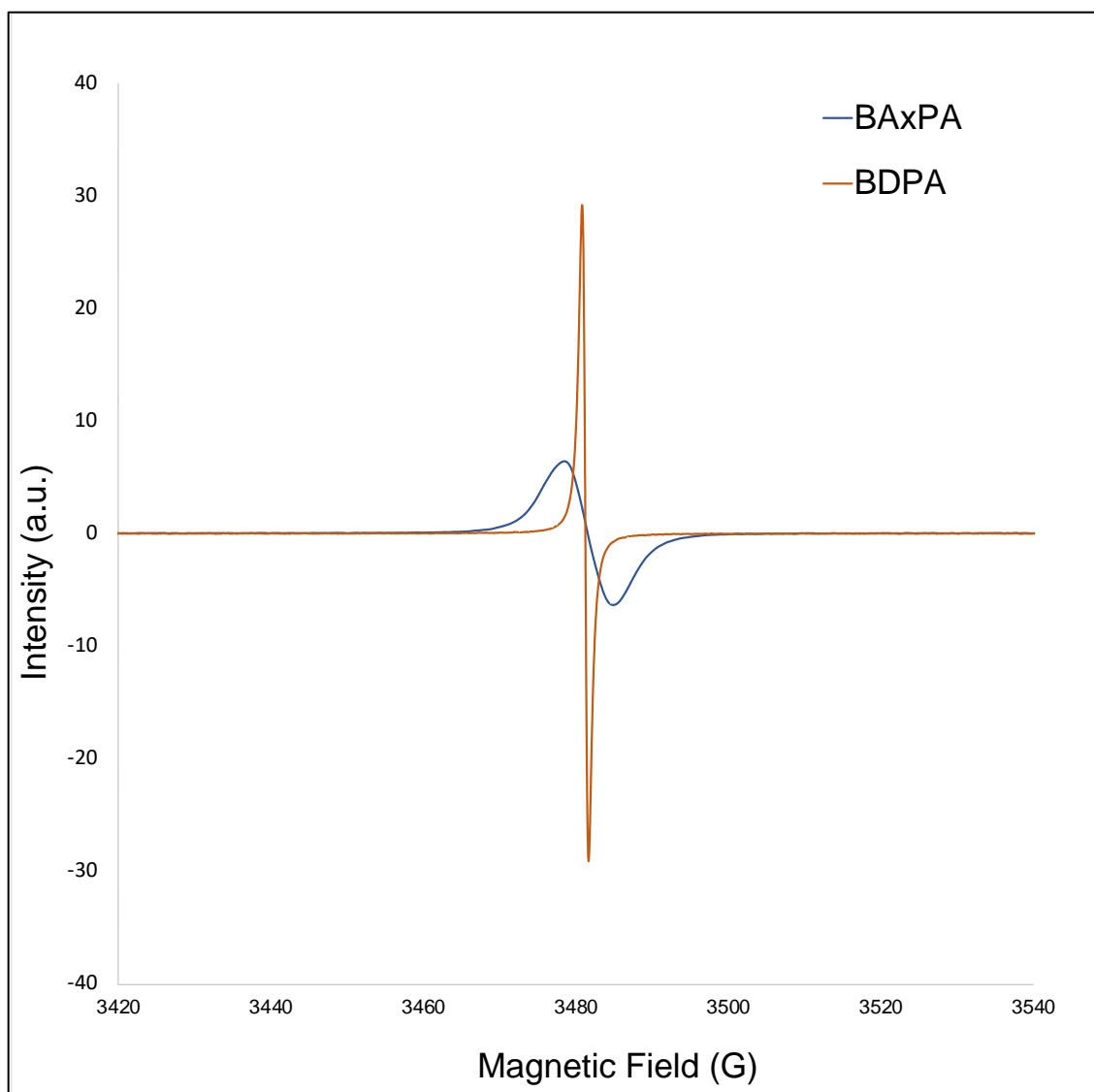


Figure 14. EPR spectrum of BAxPA and BDPA. They have similar g -values of 2.0026.

The existence of radical compound **8'** was supported by Electron Paramagnetic Resonance (EPR) spectroscopy (**Figure 9**). We took EPR measurements and received a signal between 3470 G-3481 G. We found a g -value of 2.0026 which is in accordance with the g -value of BDPA.³⁹ This g -value is expected since there are only carbons, hydrogens, a nitrogen, and an oxygen atom in the molecule. Using previously acquired EPR data of BDPA, we compared the two EPR spectra and saw quite a few differences (**Figure 10**). The unpaired electron in BDPA possesses s-orbital

symmetry and is therefore isotropic since the electronic density remains spherical regardless of the direction of the applied magnetic field. This is explained by the symmetry of BDPA as the electronic delocalization is equal throughout the molecule. Accordingly, BAXPA also has s-orbital shaped electron density (**Figure 15**). However, we saw line broadening of our BAXPA spectra potentially alluding to the anisotropy of BAXPA, meaning the electron density changes as it interacts with the applied magnetic field. The spherical spin density changes to a football shape and thus we have elongation due to anisotropy.

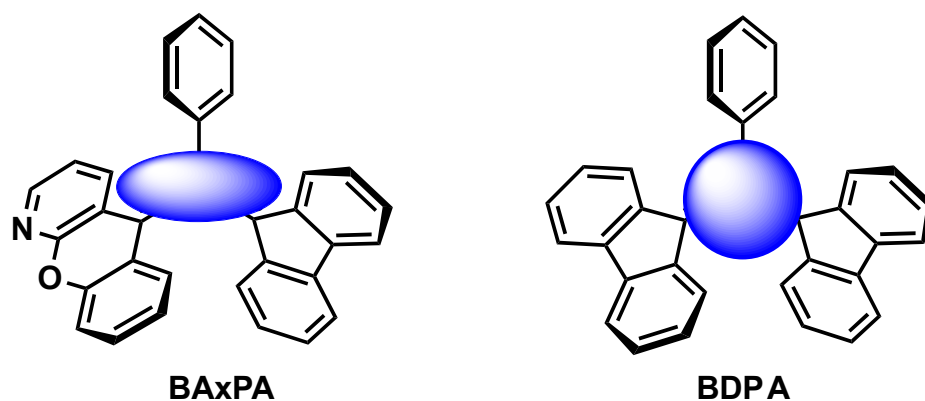


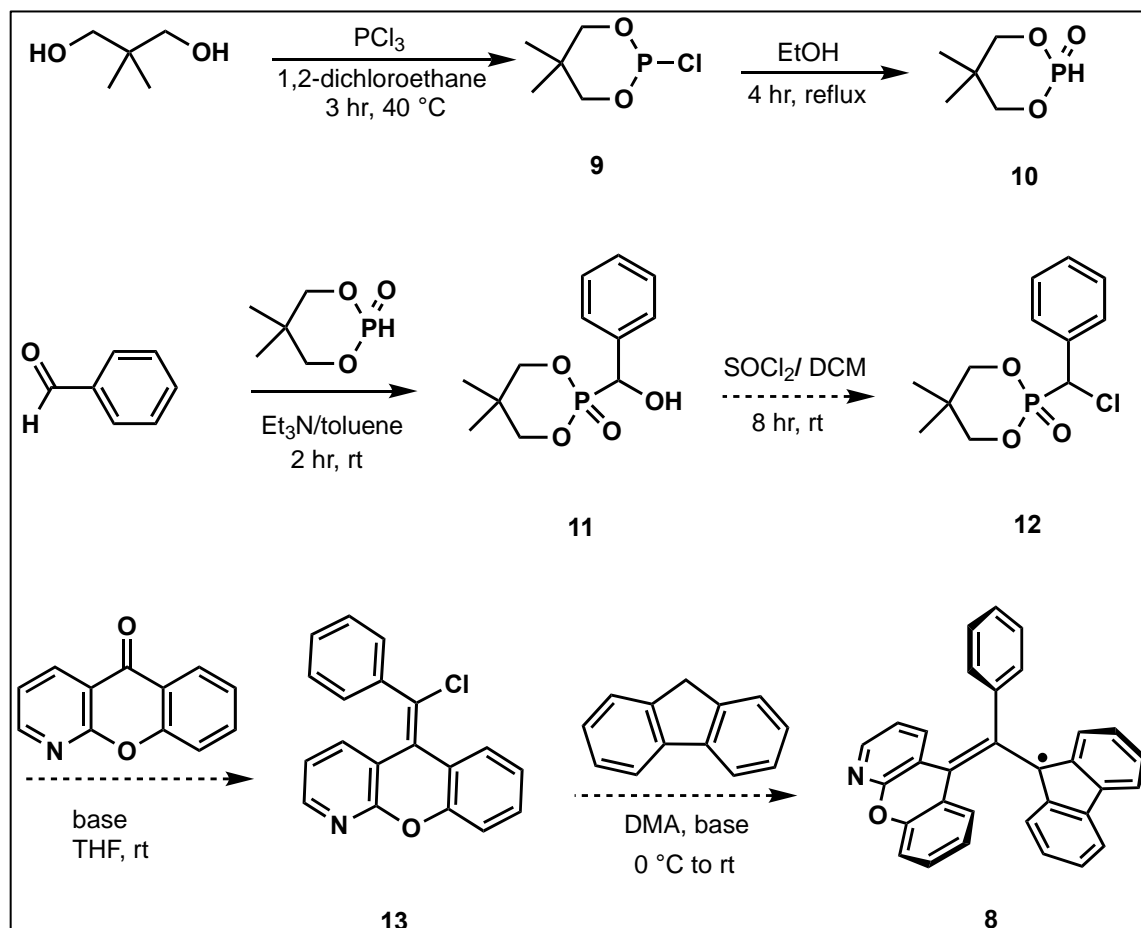
Figure 15. Spin-density of the allyl carbons in BAXPA and BDPA. BAXPA has an anisotropic spin-density and BDPA has an isotropic spin-density.

A successful HWE reaction was conducted, but the low yields meant the ketone is too inactive and not all the starting materials underwent the nucleophilic attack necessary to create the ylide. There is enough steric hindrance and electronic repulsions that lead us to believe there is not enough space to allow the facile creation of the new double bond. We believe the reaction is limited by the electronic repulsions between the 4,6-hydrogen atoms on azaxanthone and the ethoxy groups on the phosphonate (compound **5** in **Scheme 4**). We believe a new synthetic route for the HWE reaction should be used to produce BAXPA.

Conclusion

A New Approach

In our effort to improve yields of compound **6** (Scheme 4) we began pursuing a new Pudovik synthon (compound **11** in Scheme 5).⁴⁰ Fan et al. provided a facile synthesis of phosphonate **10** by a careful addition of PCl_3 in 1,2-dichloroethane, and a subsequent heating at 40 °C for three hours (Scheme 5).⁴⁰ The phosphonate was subjected to a Pudovik reaction and compound **11** was produced in quantitative yields. A subsequent chlorination of the compound **11** results in compound **12**.

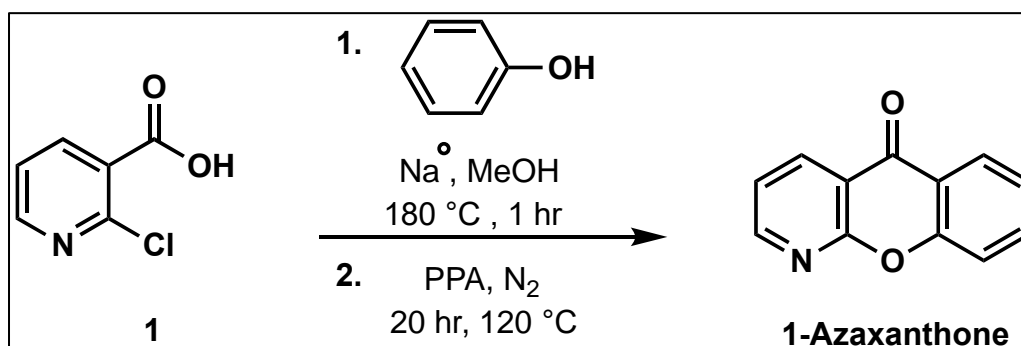


Scheme 5. Proposed synthetic strategy of BAXPA using Kumara Swamy's pinned back α -halogen Vinylphosphonate (compound **11**).⁴¹

Compound **12** is the analog of compound **5** and has been identified to be the pinned back towards the olefination reaction. It is our hope and aspiration to use this mechanism for quantifiable yields of BAxPA.⁴¹

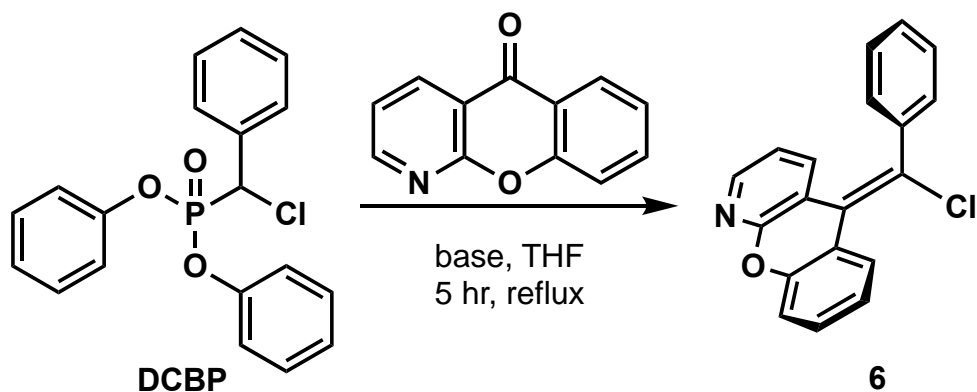
Methods

Synthetic Strategy for 1-Azaxanthone



Scheme 6. Synthetic Strategy for 1-Azaxanthone

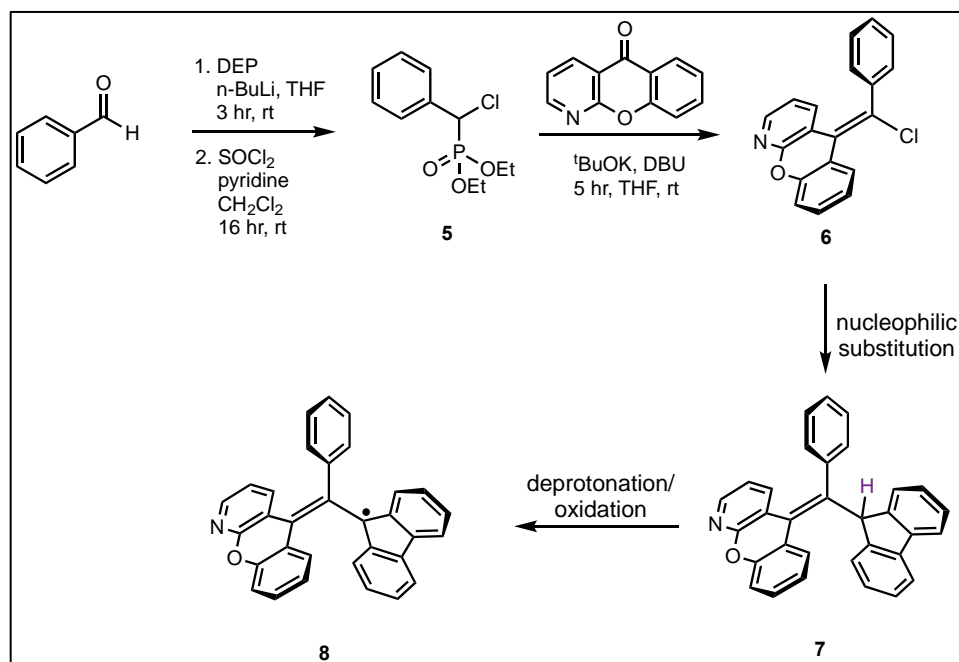
1-Azaxanthone (3): To an oven-dried Schlenk flask compound **1**, sodium metal, and phenol are mixed in anhydrous methanol under an inert atmosphere for two hours at room temperature. The mixture is then heated to 180 °C and extracted to afford a yellow/white solid with 26% yields. Compound **2** was then added to and polyphosphoric acid were added and mixed at 120 °C for 20 hours. The mixture is cooled to room temperature and 50g of ice were added and stirred until it reached room temperature. The solution is then cooled to 0 °C and basified to a pH of 12 using 50% KOH. The compound precipitated as a white solid and was recovered by vacuum filtration. The solid was recrystallized from ethanol which gave a white or yellow solid at 19% yield.



Scheme 7. General Synthetic Olefination Procedures for HWE Products

Compound 6: Diphenyl alpha-Chlorobenzylphosphonate (Scheme 3) is added to a Schlenk flask with 1-azaxanthone. A strong base of either NaH, KOH with 18-crown-6, or *t*BuOK. The mixture was left stirring at temperatures ranging from room temperature to 60 °C. TLC and NMR spectroscopy showed the anion of diphenyl alpha-chlorobenzylphosphonate, but no product.

Synthesis of BAXPA Using an Ethoxy Phosphonate Pudovik Synthon

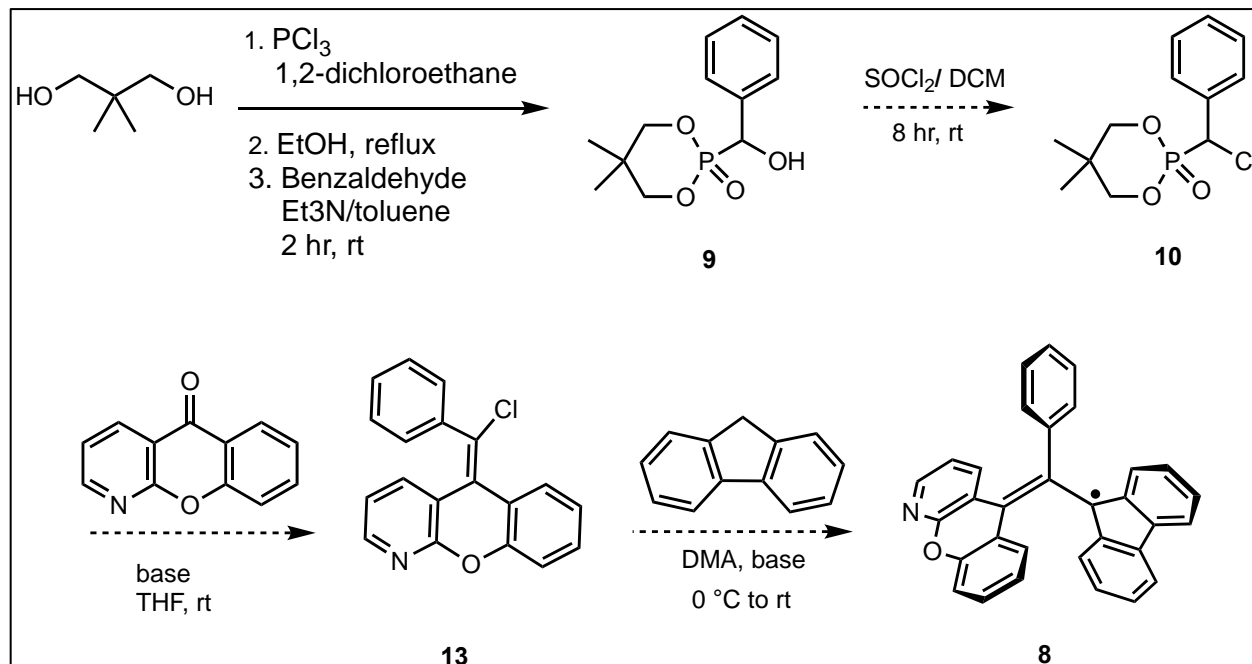


Scheme 8. Synthetic Strategy for BAXPA Proposed by Swager et al.

Compound 5: To an oven dried-Schlenk flask benzaldehyde, diethyl phosphite, and anhydrous THF were combined. Tert-butyl lithium was added dropwise, and the solution was left to stir for three hours at room temperature. Deionized water was added to quench the reaction and the solvent was removed using a rotary evaporator. The residue was extracted with CH₂Cl₂, dried over sodium sulfate and recovered by vacuum filtration. The solvent was recovered using a rotary evaporator and the residue was purified by column chromatography (CH₂Cl₂/EtOAc = 20/1). The compound was recovered as a white solid at 95%-97% yields. To an oven-dried Schleck flask compound 4, pyridine, and anhydrous CH₂Cl₂ were added. Thionyl chloride was added dropwise, and the reaction was mixed for 14 hours. Deionized water was added to quench the reaction and the solvent was removed using a rotary evaporator. Compound **5** was collected and purified by column chromatography (Hexanes/EtOAc= 3/1).

Diphenyl alpha-Chlorobenzylphosphonate precursor synthon: To an oven-dried Schlenk flask compound 5, azaxanthone, potassium tert-butoxide, DBU, and anhydrous THF were mixed. The solution was left to stir at room temperature for five hours. TLC and NMR spectroscopy showed no change from the starting materials and thus no quantifiable product was isolated.

Synthesis of α -hydroxy and α -halogen Vinylphosphonate



Scheme 9. Synthetic Strategy for BAxPA using a Vinylphosphonate

New Synthetic Pathway for compound 9: Neopentyl glycol was added in to a 100 mL round-bottom flask and stirred in 1,2-dichloroethane for 30 minutes. The flask was cooled to 0 °C and PCl_3 was added dropwise. The mixture was cooled to room temperature and heated at 40 °C for three hours. EtOH was added dropwise, and the solution was refluxed for four hours. The residue was isolated via column chromatography at 15% yield. The product was reacted with benzaldehyde, Et_3N , and toluene. The mixture was stirred for two hours at room temperature. Compound **9** was isolated as a white solid.

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