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Project Title: Synthesis of Polycyclic Aromatics via Domino Aryne Cascade Reactions

Principal Investigator: Patrick H. Willoughby, Ripon College

Progress of Research:

Overview: The UR grant provided by the ACS PRF has allowed us to develop novel synthesis methodology for the preparation of a diverse range of aryl phosphonates. Aryl phosphonates are an important class of compounds with applications in organometallic chemistry, medicinal chemistry, materials science, and agricultural chemistry. We have been developing methodology for the synthesis of aryl phosphonates from phosphorous-containing benzyne intermediates. The general strategy (cf. Figure 1) involves generating a highly reactive 2-phosphonyl benzyne intermediate from a 2-silyl-3-trifloxy aryl phosphonate. The electrophilic phosphorous-containing intermediate is subsequently “trapped” by aryneophiles to form structurally diverse and functionally dense aryl phosphonates.

Synthesis of Aryne Precursors: Among the numerous strategies for generating arynes, use of a fluoride reagent to eliminate an ortho-silyl triflate moiety from an arene is highly reliable. With this in mind, we focused our efforts on preparing aryl phosphate 3 (cf. Figure 2), which has the requisite 2-silyl-3-trifloxy functionality. Not surprisingly, this proved to be a challenge using conventional techniques (e.g., metal-mediated arene phosphonylation). However, we identified transition metal free conditions to accomplish the synthesis of 3 from readily available precursors 1 and 2 (cf. Figure 2). 2-iodo bis(trifloxy) arene 1 is available in three steps from resorcinol, and O-trimethylsilyl phosphite 2 is prepared from the corresponding dialkyl phosphite. After extensive optimization, we found that treating a mixture of 1 and 2 with a Grignard reagent gave the desired product, 3, in useful yields. The synthesis of 3 has been accomplished on a 10-gram scale without a reduction in isolated yield.

Generation of 3-Phosphonyl Benzyne: To demonstrate that the proposed aryne precursor is capable of generating a 2-phosphonyl benzyne intermediate, we added cesium fluoride to a mixture of 3 and an aryne “trap.” To simplify analysis of the resulting product mixture, our early studies have involved symmetric diene trapping agents. Use of furan and N-Boc pyrrole as the benzynie trapping agent gave the corresponding [4+2] adducts in high isolated yields, indicating that the proposed 3-phosphonyl aryne is efficiently generated from 3 in the presence of CsF. In addition to the diene trapping agents, we found that azide readily underwent an aryne click reaction when mixed with 3 and treated with CsF. Interestingly, the regioselectivity of the [3+2] cycloaddition was poor and gave a mixture of isomeric benzotriazoles that favored formation of the more sterically congested product. In future studies, we will use DFT computations to evaluate various aspects of the reaction between a 3-phosphonyl benzyne and benzyl azide. This will allow us to design substrates with more controlled regioselectivity for either isomer. Such studies will also allow us to screen more complex trapping agents to expand the scope of accessible aryl phosphonates.
Precursor Scope: Having established that treating 3 with CsF is capable of efficiently generating a 3-phosphonil benzyne, we turned to investigating the scope of the 3-phosphonil aryne precursors that could be prepared using our newly developed methodology. Thus far, we have prepared several analogues of arene 1 and O-trimethylsilyl phosphite 2 (cf. Figure 4). Variants of 1 with alkyl, aryl, and halo functionalities readily formed the corresponding aryne precursor (i.e., 3). Future studies will involve expanding the number of 1’ substrates to include more structurally complex arenes and heteroarenes. Changing the ethyl groups in O-trimethylsilyl phosphite 2 for other alkyl groups also gave the desired precursors, allowing for introduction of structural diversity about the phosphonil moiety. The diphenoxo variant also provided product, albeit in lower yields. We attribute the reduced efficiency of aryl esters of phosphorous(V) agents to them being more prone to reaction with Grignard reagents. In future studies, we will assess the viability of other O-trimethylsilyl phosphorous(III) reactants, including, for example, those prepared from diaryl secondary phosphate oxides and enantioenriched phosphites (e.g., those derived from BINOL and TADDOL). Use of enantioenriched chiral O-trimethylsilyl phosphites will allow us to investigate the stereoselectivity of the reaction at the phosphorous(V) atom. Furthermore, the resulting P-stereogenic products could potentially impose stereoselectivity in subsequent, stereocenter forming aryne trapping reactions (e.g., [4+2] cycloaddition with furans and pyrroles).

Impact of the Research on PI Career:

The ACS PRF UR grant allowed the PI to identify new conditions for the synthesis of trisubstituted aryl phosphonates that are capable of forming a 3-phosphonyl benzyne. Manuscripts that discuss these results are in preparation, and the early results will be presented at an upcoming ACS regional meeting. Experience from this new direction has the laid foundation for expanding our research program to include synthesis methodology involving other types of silyl transfer reactions for preparing other unusual aryne precursors. Additionally, future studies will include developing benzyne “trapping” methodology that is unique to 3-phosphonyl arynes. The supported project has further allowed the PI to begin expanding his research program to include studies of materials developed using the newly prepared and structurally interesting phenyl phosphonates.

Impact of the Research on Careers of Participating Students:

The ACS PRF UR grant supported summer stipends for three undergraduate research students. The students’ careers were positively impacted by the extensive experience they gained in organic synthesis research. Students were involved in all aspects of the research described in this progress report. Specially, each synthetic step of the project required that students optimize the reaction conditions and explore the scope of amenable substrates. This project involved becoming adept with handling moisture sensitive reagents on a micromolar scale. Students purified the newly prepared products using flash chromatography and worked with the PI to elucidate the structure using NMR spectroscopy and LC/MS. Students fully characterized all unreported compounds and worked with the PI to record the plethora of analytical data [i.e., high resolution ESI-MS, IR spectroscopy, and ($^1$H, $^{13}$C, $^{19}$F, $^{31}$P) NMR spectroscopy] in a format suitable for inclusion in ACS journals. Collectively, the techniques that the ACS PRF-supported students practiced this past summer will allow them to stand out in future laboratory careers.

In addition to gaining laboratory experience in organic synthesis, the students worked with the PI to develop new methodology for the synthesis of aryl phosphonates using the ideas captured in the original grant proposal. Students assisted the PI with reviewing previous results from the literature, revising approaches that were included in the original project proposal, and designing experiments to test the new hypotheses. These outside-the-lab experiences will benefit students in their future, post-undergraduate research careers, which will undoubtedly involve reevaluating proposed ideas and designing new experiments to probe revised hypotheses.

Results obtained from the supported studies will be presented by the participating students at an upcoming National ACS meeting. Attending these types of meetings will positively impact the careers of the students by providing numerous experiences to talk about their research experience with other chemistry professionals. Additionally, feedback received from these conversations will be useful in advancing the students’ research projects.