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# A one-pot method for the preparation of 2,5-diarylthiophene-1oxides from arylacetylenes

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# ABSTRACT

2,5-Diarylthiophene-1-oxides have been prepared from readily available arylacetylene precursors via zirconacyclopentadiene intermediates. The isolated yields of the desired thiophene-1-oxides are comparable to those obtained from the oxidation of thiophene derivatives while avoiding the formation of over-oxidation products. Furthermore, this route offers broader versatility than commonly used methods by providing products outfitted with electron-donating or electron-withdrawing groups with very little variation in isolated product yields. Finally, this strategy provides access to products containing functional groups that are not compatible with oxidation conditions.

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The [4+2] cvcloaddition reaction-commonly known as the Diels-Alder reaction-has had a profound effect on synthetic organic chemistry due to its ability to generate 6-membered rings with high regio- and stereochemical control.<sup>1</sup> As a result, the reaction has found utility in areas ranging from natural product synthesis<sup>2</sup> to the preparation of organic materials.<sup>3</sup> Of particular interest to the field of polycyclic aromatic hydrocarbons (PAHs) are cyclic dienes that undergo Diels-Alder reactions with alkynes then subsequently fragment to produce substituted benzene rings in a single synthetic step. Although there is potential for dienes outfitted with aryl groups at the 1- and 4-positions to act as synthons for the fabrication of PAHs, such compounds are surprisingly uncommon. While 2,5-diarylated thiophene, thiophene dioxides, and furans are synthetically accessible, these compounds typically require the use of strongly activated dienophiles or forcing conditions (high temperatures and/or pressures) to react by cycloaddition.<sup>4</sup> Cyclopentadienone and isobenzofuran derivatives are inherently more reactive but synthesizing the 2,5-diarylated analogs of these compounds without additional substituents is nearly impossible.<sup>5</sup> Thiophene-1-oxides,<sup>6</sup> originally identified as intermediates in the oxidation of thiophenes to thiophene dioxides, on the other hand, have recently shown the potential to behave as highly reactive dienes in the synthesis of PAHs.<sup>7</sup> Despite these recent advances, however, these dienes have yet to find widespread utility, likely as a result of the absence of methodology capable of consistently

providing functionalized derivatives. To remedy this situation we have developed a one-pot strategy that converts easily accessible arylacetylenes into 2,5-diarylthiophene-1-oxides. Importantly, the yields achieved through this process are comparable to those achieved through the most commonly used oxidation strategies, but with a much higher functional group tolerance.

Thiophene-1-oxides are commonly synthesized through the oxidation of the corresponding thiophene derivative. The earliest example of this strategy employed *m*-chloroperoxybenzoic acid (*mCPBA*) as the oxidizing agent, however, this could only provide thiophene-1-oxides bearing bulky substituents (in order to prevent self-dimerization) in very low yields (~5%); the majority of the material recovered from these reactions being the sulfone—the product of over-oxidation.<sup>8</sup> It was later realized that the introduction of either a strong Brönsted–Lowry<sup>9</sup> or Lewis acid<sup>10</sup> to the oxidative conditions hinder the over-oxidation process resulting in an improvement in reaction yields. In our studies, we were







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Table 1Reaction substrate scope



<sup>&</sup>lt;sup>a</sup> Isolated yield obtained by quenching with thionyl chloride.

<sup>b</sup> Isolated yield obtained by quenching with SO<sub>2</sub>.

surprised to find, however, that these oxidation strategies were intolerant of a variety of functional groups installed on the aryl rings of 2,5-diarylthiophenes, *most notably* alkoxy and alkyl moieties. Furthermore, for the compounds that could be successfully oxidized, the reactions had to be monitored closely to limit the formation of the sulfone and as a result the yields of these reactions varied significantly. An alternate strategy for the synthesis of thiophene-1-oxides relies on the reaction of zirconacyclopentadiene precursors with either thionyl chloride<sup>11</sup> or sulfur dioxide.<sup>12</sup> This method is particularly attractive as it avoids the undesired over-oxidation discussed above and exhibits a greater functional group tolerance. Although a vast array of metallole heterocycles have been derived from zirconacyclopentadiene intermediates,<sup>11,13</sup> these reactions almost exclusively employ disubstituted acetylenes for the generation of tetrasubstituted species. Terminal acetylenes, on the other hand, have only been employed on a handful of occasions<sup>14</sup> likely due to the fact that such systems have been observed to lead to mixtures of the regioisomeric 2,4- and 2,5-disubsituted products.<sup>15</sup> Surprisingly, the conditions presented herein produce only the 2,5-diarylated product and we did not observe any of the undesired isomers from our reactions mixtures.<sup>16</sup>

A simple example of the one-pot synthesis of 2,5-diarylthiophene-1-oxides is displayed in Scheme 1. Initially, 'Cp<sub>2</sub>Zr' was generated by the slow addition of *n*-BuLi to Cp<sub>2</sub>ZrCl<sub>2</sub> at -78 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature until a dark red solution developed. Phenylacetylene (**1a**) was then added at 0 °C to generate the diphenylzirconacyclopentadiene intermediate (**2a**). The reaction mixture was then cooled back down to -78 °C and thionyl chloride was added drop-wise to the reaction mixture affording a bright yellow solution. The cold reaction mixture was directly added to a plug of silica and the product (**3a**) was eluted in 30% yield (Table 1, entry 1).

It is important to note that our initial attempts to perform these reactions using standard Negishi workup conditions resulted in surprisingly low (ca. 5%) yields of the desired thiophene-1oxides.<sup>17</sup> Additionally, crude reaction mixtures that were left in a -20 °C freezer overnight were devoid of the desired product upon subsequent analysis. We suspect that byproducts resulting from the thermal decomposition<sup>18</sup> of the 'Cp<sub>2</sub>Zr' (namely 1-butene and cyclopentadiene), are capable of reacting in a Diels-Alder fashion with our desired product. Unfortunately, we were unable to confirm the existence of such adducts through mass spectral analysis of the crude reaction mixture. Nonetheless, considerably better yields can be achieved by filtering the cold reaction mixture through a plug of silica and eluting any potentially reactive intermediates with hexanes prior to isolating the desired compound using more polar eluents. The isolated products undergo slight decomposition when left in organic solvents for extended periods of time but they can be stored as solids at 0 °C for months with little to no decomposition.

Having established that the desired reactivity could be achieved we were excited to find that the reaction is tolerant of a range of electronically diverse functional groups, as observed in Table 1. When electron-donating functionality was introduced to the para position of the aryl ring of the arylacetylene-such as the methyl (1b) and methoxyl (1c) substituted derivatives—we observed the formation of products 3b and 3c in yields that were nearly identical to that of the unsubstituted precursor (3a). When the methoxyl group is shifted meta to the alkyne (1d), where it is theoretically less able to donate electron-density into the triple-bond, surprisingly no decrease in yield is observed. Even the veritrole-based system (1e) equipped with two electron-donating methoxyl groups displays only a minor increase in the yield of **3e** compared to the less electron-rich systems. At the opposite end of the spectrum. we observe a slight but significant decrease in the yield when mildly electron-withdrawing fluorine groups are installed on the aryl ring (1f) and a complete loss of reactivity when nitro groups are incorporated (1g). To investigate this observation we used density functional theory (DFT) calculations to generate electrostatic potential maps (see Supporting information) of each of the arylacetylenes listed in Table 1.<sup>19</sup> These maps indicate the presence of a distinctly negative environment surrounding the alkyne for each of the compounds *except* for **1g**, which has a noticeably positive electrostatic potential surrounding the triple bond. Based on this evidence, it is reasonable to conclude that the strongly electron-withdrawing nature of the nitro group renders the alkyne sufficiently electron-poor such that it is unable to react with the generated 'Cp<sub>2</sub>Zr' species.

Substrates **1h** and **1i** further demonstrate the utility of this methodology. The *o*-chloro derivative **1h** illustrates that substituents *ortho* to the alkyne have little impact on the reaction yield due to steric effects. Furthermore, due to the position of the chlorine atom on this substrate it has the potential to find significant utility in generating fused ring systems through sequential Diels–Alder/palladium-catalyzed arylation reactions as we recently demonstrated in the synthesis of tetrabenzo[8]circulene.<sup>7a</sup> In a similar vein, the brominated derivative, **1i**, illustrates that more reactive halides survive the reaction conditions with no observable decrease in yield. Such functional groups have the potential to provide a synthetic handle for further transformations through metal-catalyzed cross-coupling reactions.

Finally, in addition to phenyl-substituted thiophene-1-oxides, mixed thiophene/thiophene-1-oxides are an attractive synthetic target as such structures cannot be obtained though the traditional oxidation procedures. Surprisingly, while we were able to observe the conversion of 2-ethynylthiophene (**1j**) into the desired compound (**3j**), the formation of a complex mixture of products made it particularly challenging to isolate the desired product. However, replacing thionyl chloride with SO<sub>2</sub> produced a much cleaner reaction and allowed us to isolate the desired product in 10% yield (entry 9).<sup>20</sup> To our knowledge this is the first report of a thiophene/thiophene-1-oxide oligomer that is free of substituents at the 3- and 4-positions of each of the thiophene rings.

In summary, we have presented a convenient one-pot method for the synthesis of 2,5-diarylthiophene-1-oxides. This transformation avoids the problematic formation of 1,1-dioxides that result from oxidation strategies while providing the desired products in comparable yields. The methodology discussed in this Letter is tolerant of an array of electron-donating and electron-withdrawing functionalities, halogens, substituents positioned in sterically demanding positions, and functional groups that would not be tolerant of oxidation conditions.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03. 051.

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- 16. The position of the aryl substituents on each of the thiophene-1-oxide products was confirmed using Heteronuclear Single Quantum Coherence (HSQC) spectroscopy. The carbon alpha to the sulfoxide on the thiophene-1-oxide ring has a characteristic downfield shift of ca. 150 ppm and for each substrate it was confirmed that this carbon atom was not directly attached to a proton. HSQC are provided in the SI.
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- Electrostatic potential maps were generated using DFT calculations (B3LYP functional, LACVP<sup>\*\*</sup> basis set for bromine and 6-31G<sup>\*\*</sup> basis set for all other atoms) performed using Jaguar (see Jaguar: Version 8.3, Maestro: Version 9.8, Schrödinger, LLC, New York, USA, **2014**) software package.
- 20. Despite reports that the yields of similar systems were increased by replacing thionyl chloride with sulfur dioxide (see Ref. 12a) this was not observed for our substrates. However, reactions carried out under these conditions tended to afford notably cleaner crude reaction mixtures.