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Paul J. Griffin, Matthew A. Fava, St. John T. Whittaker, Kristopher J. Kolonko, Arthur J. Catino

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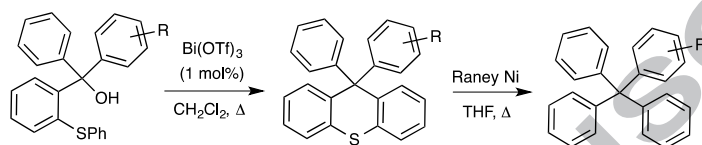
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## Synthesis of tetraarylmethanes *via* a Friedel-Crafts cyclization/desulfurization strategy

Paul J. Griffin<sup>a</sup>, Matthew A. Fava<sup>a</sup>, St. John T. Whittaker<sup>a</sup>, Kristopher J. Kolonko<sup>b</sup>, and Arthur J. Catino<sup>a\*</sup>

<sup>a</sup>Department of Chemistry, The University of Scranton, Scranton, PA 18510 USA

<sup>b</sup>Stewart's Advanced Instrumentation and Technology (SAInT) Center, Siena College, Loudonville, NY 12211 USA

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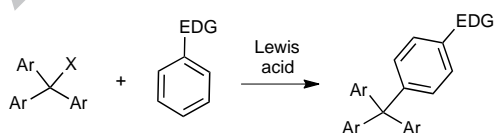
desulfurization

### ABSTRACT

Tetraarylmethanes are an important class of molecules that contain four aryl groups bonded to a central carbon atom. The shape/three-dimensionality of these molecules makes them suitable for organic light-emitting diodes (OLEDs), organic solar cells, hydrogen storage, and even drug-delivery. Despite their importance, there are only a few methods available for their preparation. Herein, we report a simple procedure for the preparation of tetraarylmethanes that involves a bismuth-catalyzed Friedel-Crafts cyclization followed by a desulfurization reaction mediated by Raney nickel.

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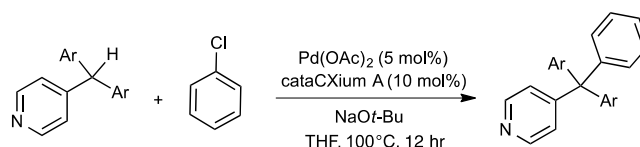
Tetraarylmethanes contain four aryl groups (typically phenyl) bonded to a central carbon atom. The shape/three-dimensionality of these molecules has made them suitable for organic light-emitting diodes (OLEDs),<sup>1</sup> organic solar cells,<sup>2</sup> hydrogen storage,<sup>3</sup> and even drug-delivery.<sup>4</sup> Despite their importance, there are only a few methods available for their preparation. The most commonly used method involves Friedel-Crafts addition to a triaryl halomethane mediated by a Lewis acid (Fig. 1).<sup>5,6</sup> A major limitation of this method is that the aryl group must be substituted with a strong electron-donating group (EDG). As this group is typically unwanted, additional steps are required to remove it. Another drawback is that only *para*-substituted tetraarylmethane products can be obtained either in the Friedel-Crafts reaction or in subsequent reactions.



**Figure 1.** Preparation of tetraarylmethanes by Friedel-Crafts addition to triaryl halomethanes.

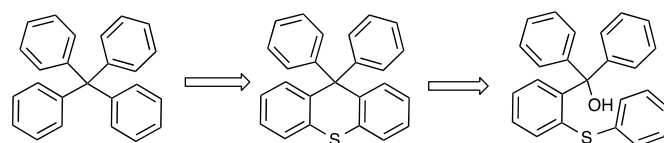
Recently, chemists have begun exploring transition metal cross-coupling as a viable strategy to prepare these compounds.<sup>7</sup> A notable example was reported by Walsh and Mao in 2017 in which various triaryl motifs containing a benzylic proton were used with palladium catalysis to construct tetraarylmethanes (Fig. 2).<sup>8</sup> Although this was a major step toward a general method, it requires one aryl group

to be a pyridine (or a related heterocycle) and does not allow access to simple substituted tetraphenylmethanes.



**Figure 2.** Synthesis of tetraarylmethanes *via* palladium-catalyzed cross-coupling reported by Walsh and Mao.<sup>8</sup>

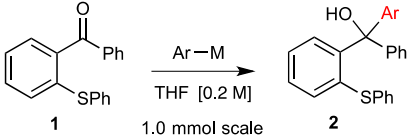
Our strategy to prepare tetraarylmethanes with all phenyl groups and diverse substitution/electronics was to expand upon the Friedel-Crafts addition by performing the reaction *intramolecularly*. We were particularly attracted to triaryl-methanols containing a sulfur-tethered benzene moiety (Fig. 3). The close proximity of the tethered benzene to the site of attack and the formation of a thermodynamically favorable thioxanthene ring would eliminate the need for strong electron-donating groups and harsh reaction conditions. Subsequent removal of the sulfur atom by conventional methods<sup>9</sup> would then provide the tetraarylmethane.



**Figure 3.** Synthetic plan to prepare tetraarylmethanes *via* Friedel-Crafts cyclization/desulfurization (this work).

We began our study by preparing a variety of 2-thiophenyl triarylmethanols using a modified procedure reported by Shimizu and co-workers (Table 1).<sup>10</sup> Treatment of 2-thiophenylbenzophenone<sup>11</sup> with an aryl Grignard reagent in THF at reflux gave the corresponding triarylmethanol in poor to moderate yield. We found that the reaction was sensitive to the electronic nature of the aryl Grignard reagent with those containing electron-donating groups giving the lowest yields. Analysis of the crude reaction mixture revealed a significant amount of biphenyl products derived from nucleophilic aromatic substitution of the Grignard followed by loss of thiophenolate. This side reaction could be mitigated by using electron-deficient aryl Grignard reagents (Entries 10 and 11); however, no reaction was observed with trifluoromethyl- and perfluoro-aryl Grignard reagents (Entries 12 and 13). These results led us to consider “harder” nucleophiles to enhance reactivity at the carbonyl group. Gratifyingly, aryl lithium reagents, prepared *via* metal-halogen exchange from the corresponding bromides, performed very well across a range of substituents. During the course of optimization we found that the highest yields were obtained when a solution of 2-thiophenyl-benzophenone was added immediately after aryl lithium formation at -78 °C. Allowing the aryl lithium reagent to warm to 0 °C followed by addition of the benzophenone gave lower yields and increased biphenyl formation.

**Table 1.** Synthesis of triarylmethanol starting materials

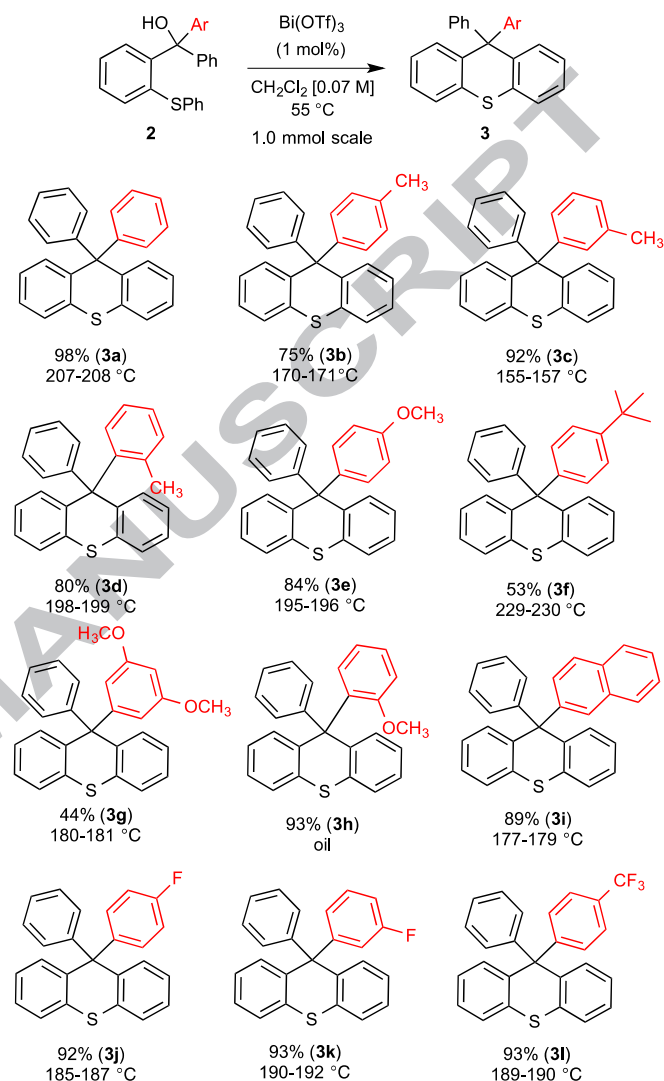


Entry	Ar	M = MgBr <sup>a</sup> yield <b>2</b> (%)	M = Li <sup>b</sup> yield <b>2</b> (%)
1	C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )	66	80
2	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	48	83
3	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	68	94
4	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	55	94
5	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	28	56
6	4- <i>t</i> -Bu-C <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	26	55
7	3,5-(OCH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	54	82
8	2-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	37	85
9	2-naphthyl ( <b>2i</b> )	55	98
10	4-FC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	83	83
11	3-FC <sub>6</sub> H <sub>4</sub> ( <b>2k</b> )	75	95
12	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2l</b> )	nr	61
13	C <sub>6</sub> F <sub>5</sub>	nr	nr

<sup>a</sup>Reactions were conducted using 2.5 equivalents of arylmagnesium bromide in THF at reflux for 3-8 hours. <sup>b</sup>Reactions were conducted using 2.5 equivalents of aryllithium in THF at -78 °C for 5-10 minutes. Percent yields are for isolated products and “nr” refers to no reaction.

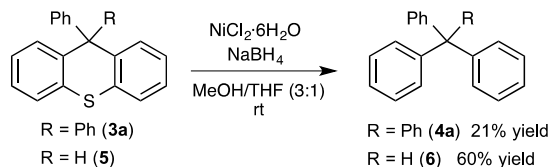
With a variety of triarylmethanols in hand, we explored conditions for the subsequent Friedel-Crafts cyclization to form 9,9-diarylthioxanthenes (Fig. 4). It was previously reported that the cyclization of **2a** can be accomplished with sulfuric acid in acetic acid at reflux.<sup>10</sup> Seeking milder conditions that would tolerate a wide range of substitution and an easier work-up, we explored catalytic Lewis acids. We ultimately found that bismuth triflate (Bi(OTf)<sub>3</sub>) in dichloromethane at reflux, as described by Rueping and co-workers for the benzylation of arenes,<sup>12</sup> gave the highest yield for the cyclization of **2a**.<sup>13</sup> Application of these conditions to the remaining triaryl-methanols proceeded smoothly to give thioxanthane ring products in good to excellent yields. The reactions were complete in 1-4 hours and the products were

isolated by filtration through a plug of silica followed by rinsing with dichloromethane. With the exception of the 2-methoxy-substituted product **3h**, all reactions gave highly crystalline products with sharp melting points after the evaporation of dichloromethane.



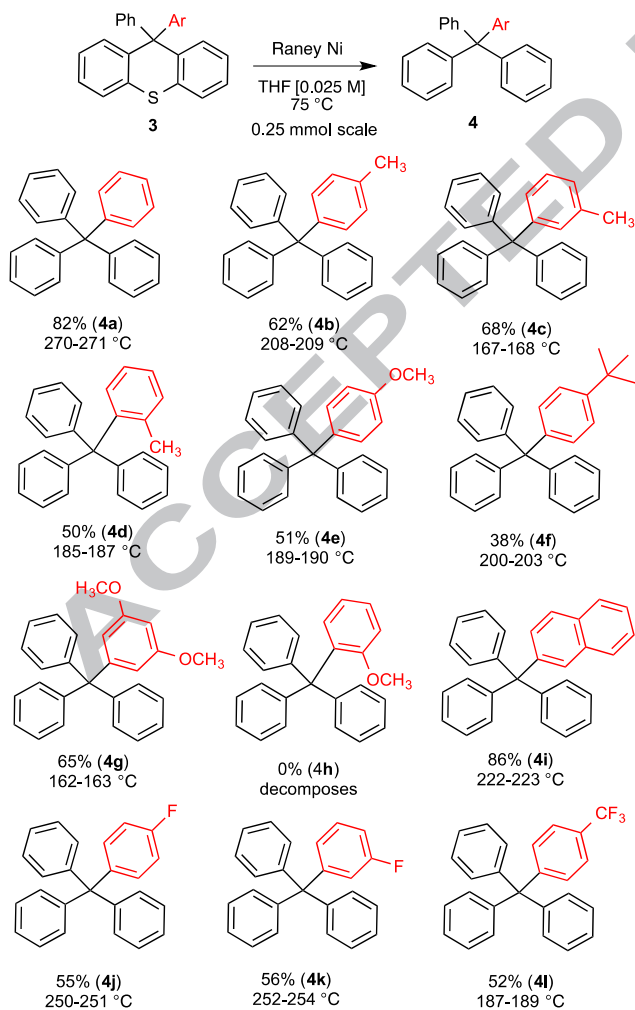
**Figure 4.** Friedel-Crafts cyclizations catalyzed by bismuth(III) triflate.

We next explored conditions to convert the 9,9-diarylthioxanthenes to tetraphenylmethanes. We were initially drawn to nickel boride, generated *in situ* from nickel chloride and sodium borohydride, for its ease of preparation and wide applicability.<sup>14</sup> As such, treatment of **3a** with nickel boride gave 21% yield of tetraphenylmethane **4a** (Fig. 5).<sup>15</sup> While troubleshooting the reaction we noted very poor solubility of both the starting material and the product in the reaction solvent. Attempts to increase the amount of THF and/or increase the temperature to enhance solubility resulted in decreased yields. To test the hypothesis that solubility was the problem and not the stability of the thioxanthene ring, we prepared 9-phenyl-thioxanthene (**5**)<sup>16</sup> and subjected it to the optimized reaction conditions (*vide infra*). Both the product and starting material are soluble in MeOH/THF (3:1). The reaction of **5** with nickel boride gave >95% conversion (60% isolated yield) of triphenylmethane (**6**).



**Figure 5.** Desulfurization of thioxanthenes mediated by nickel boride.

Based on this outcome, we turned our attention to Raney nickel, which unlike nickel boride, can function in a solely aprotic solvent such as THF. Treatment of **3a** in THF with commercially available 2800® Raney nickel slurry resulted in consumption of the starting material and only a trace amount of tetraphenylmethane. Once again, the problem was solubility, particularly that of the product (for comparison the reaction of **5** with Raney nickel gave 97% yield of **6**). Tetraphenylmethane has poor solubility in many organic solvents. Consequently, any attempt to remove the nickel residues after the reaction also removed the product. After some experimentation, we implemented a few simple procedural changes to overcome this problem. These include 1) decanting the water from the commercial Raney nickel slurry and then washing it with THF to remove any residual water, 2) conducting the reaction at 75 °C, and 3) performing a hot decantation in the workup followed by washing with hot THF and toluene for maximum extraction of the product.

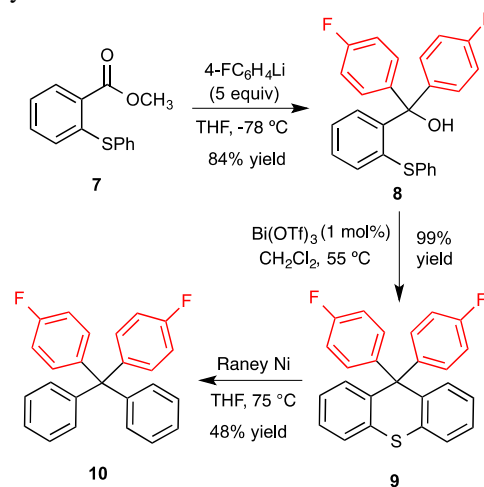


**Figure 6.** Desulfurization with Raney nickel to give various tetraarylmethanes.

With optimized reaction conditions in hand, we conducted desulfurizations across all of our 9,9-diaryltioxanthenes (Fig. 6). The reactions showed complete consumption of the starting material in 2-6 hours as judged by TLC and/or  $^1\text{H}$  NMR analysis of reaction aliquots. Isolated yields were moderate to good and in only one case failed to give the intended product. All the products were highly stable and exhibited high melting points.

Of particular note is that this method enables the synthesis of tetraphenylmethanes that contain either electron-withdrawing or electron-donating groups having *ortho*-, *meta*- or *para*-substitution (Fig. 6). Interestingly, the methyl group in tetraphenylmethane **4d** exhibits a chemical shift anisotropy of almost 1 ppm (upfield) indicating that this substituent probably resides above one of the benzene rings in the molecule.<sup>17</sup> Polycyclic aromatic compounds such as naphthalene can also be readily introduced (**4i**). A limitation of this method is the use of Raney nickel as there are functional groups that would undergo reaction.<sup>18</sup> We examined other methods for desulfurization such as with alkali-metal<sup>19</sup> or with potassium *tert*-butoxide/hydrosilane,<sup>20</sup> however, they were unsuccessful with our substrates.

Finally, we were pleased to find that this methodology can be used to prepare *bis*-substituted tetraarylmethanes (Fig. 7). For example, reaction of methyl 2-(phenylthio)benzoate (**7**)<sup>21</sup> with 4-fluorophenyl lithium (generated *in situ* by metal-halogen exchange) using our previously described conditions gave triarylmethanol **8**. Subsequent treatment with bismuth triflate followed by desulfurization with Raney nickel gave the *bis*-fluoro-substituted tetraphenylmethane **10** in good overall yield.



**Figure 7.** Synthesis of a *bis*-substituted tetraphenylmethane using the described methodology.

In summary, we have reported a general method for the preparation of tetraarylmethanes that overcomes many of the limitations in both intermolecular Friedel-Crafts and transition metal-catalyzed routes. We have shown that 2-thiophenyl triarylmethanols are readily obtained by nucleophilic addition, that a catalytic amount of bismuth triflate enables cyclization under extremely mild conditions, and that desulfurization is viable with Raney nickel to give a variety of tetraphenylmethanes. Future work will address the expansion of scope using other electrophiles that contain a sulfur-tethered benzene moiety (e.g. **7**), the development of an asymmetric variant to prepare chiral tetraarylmethanes, and the preparation of useful tetraarylmethanes for various applications.

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## Supplementary Material

Supplementary data associated with this article can be found, in the online version, at



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### Highlights

*for*

“Synthesis of tetraarylmethanes *via* a Friedel-Crafts cyclization/desulfurization strategy”

1. Tetraarylmethanes prepared with all phenyl groups and diverse substitution
2. Friedel-Crafts cyclization gives 9,9-diarylthioxanthene precursors
3. Tetraarylmethanes obtained by desulfurization with Raney nickel
4. Tetraarylmethanes with electron-withdrawing or electron-donating groups
5. Nucleophilic addition to benzophenone to form triarylmethanols