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# Synthesis of 5-phenyl-1,8-naphthalic anhydrides: An exercise in acenaphthene chemistry

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ABSTRACT

The synthesis of phenylnaphthalic anhydrides, including substitution patterns typically found in the Haemodoraceae and Pontederiacea family of plants, was explored using Suzuki and Ullmann-type aromatic substitutions on acenaphthene. Synthetic challenges were surmounted by tactical changes to determine the order of events.

Phenylnaphthalic anhydrides (phenylbenzo[*de*]isochromene-1,3-diones) are a class of compounds isolated from plants of the Haemodoraceae, Musaceae, and recently Pontederiaceae families [1]. In each family, the structural features of the members differ, creating an interesting case of positional isomerism (Fig. 1). In *Musa*, their roles as phytoalexins [1a–b] have led to synthetic efforts to prepare these compounds [2]. However, such efforts have yet to be recorded in the Pontederiaceae or Haemodoraceae, even though phenylnaphthalic anhydrides and their vinylogous analogs are involved in the defense mechanism of these plants [3].

Initially, we focused on 3,4-dimethoxy-5-phenyl-1,8-naphthalic anhydride (**1**), a moderate cytotoxic compound from *Haemodorum simplex* [1d]. Its synthesis can provide access to other natural products like 4-hydroxy-5-phenyl-1,8-naphthalic anhydride (**2a**), isolated in minute amounts (0.7 mg) from *Pontederia crassipes* Mart. (water hyacinth) [1h]. The latter furnish a suitable model for the study of a recently reported transformation between 3,4-dihydroxy-5-phenyl-1,8-naphthalic anhydride and amino acids to generate phenylcarbamoylnaphthoquinones under very mild conditions (Scheme 1) [3b]. These latter types of compounds, as members of the *p*-quinone family, incorporate an important scaffold in many natural products of biological significance with important redox properties [3c].

The intriguing mechanistic aspects of such a spontaneous cascade and the biological potential of these *N*-acylating agents drew our attention to the possibility of developing a synthesis for compounds **1** and **2a**. Herein, we report its synthesis starting from acenaphthene.

Our synthetic strategy is depicted in Scheme 2. It consists of a simple sequence of aromatic substitutions on the acenaphthene ring, followed by the oxidative unveiling of the anhydride moiety. However, the correct order of events was uncertain from the outset, and the crowded nature of the *peri*-substituted acenaphthene required consideration of reactions somewhat tolerant to steric demands. This criterion favored Suzuki coupling and copper-mediated (Ullmann-type) aromatic substitutions as trial reactions.

Initial efforts to obtain **1** commenced with acenaphthene, which was subjected to bromination [NBS, 2 eq] to afford the known 5,6-dibromoacenaphthene (**7a**) [4] in 20 % yield (Scheme 3). Sequential bromination did not improve the yield but identified the second electrophilic substitution as the cause of the problem.

Despite the low yield, 5,6-dibromoacenaphthene (**7a**) could be purified from the reaction mixture with relative ease and in gram quantities [4], a fact that encouraged further exploration towards phenyl substitution using Suzuki coupling. Unfortunately, treating **7a** with phenylboronic acid under typical Suzuki conditions [5] invariably afforded complex mixtures in which mono-debromination prevailed.

Thus, a tactical change in which a bromine atom is introduced after the arylation step was considered. The reasoning is that the ring to be attacked is less aromatic in 5-phenylacenaphthene (**6**) than in bromoacenaphthene (**7**). This allows for a more favorable process than the analog reaction on bromoacenaphthene (**7**) to give a product that exerts a similar pairwise steric *peri*-interaction of 5,6-dibromoacenaphthene (**7a**). Quantum chemistry calculations supported this idea (see Fig. 2 and supplemental info) [6].

Accordingly, Suzuki coupling between 5-bromoacenaphthene (**7**)

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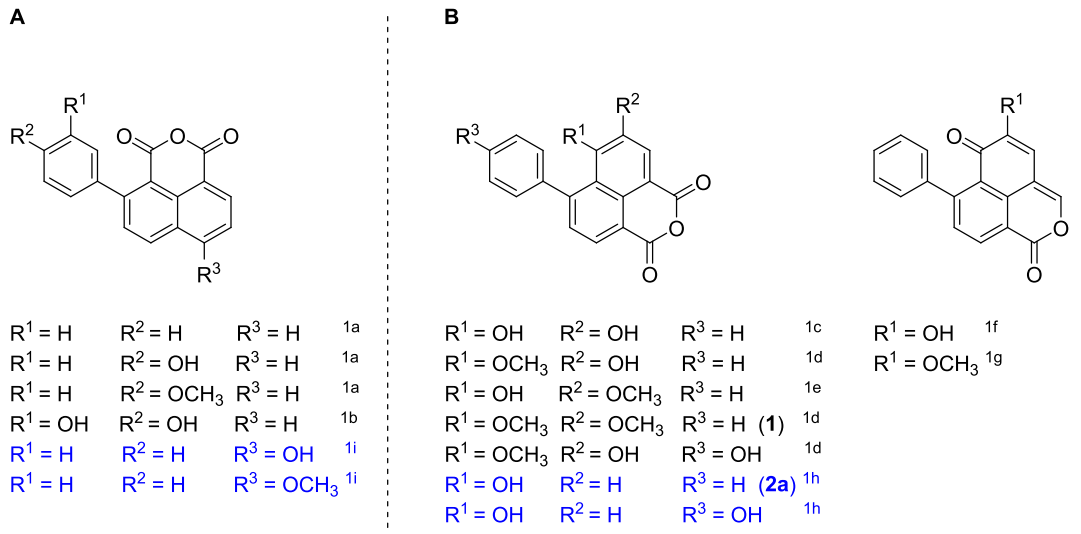
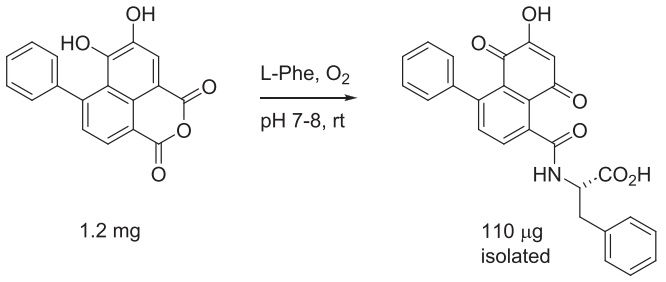


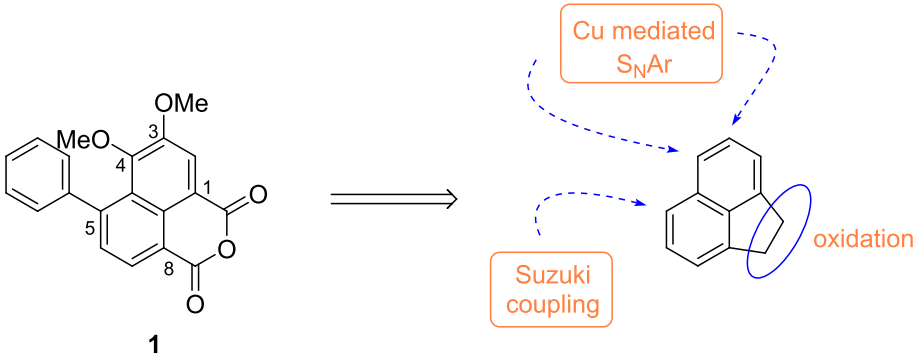

**Fig. 1.** Examples of phenylnaphthalic anhydrides and vinylogous analogs isolated from Musaceae (A), Haemodoraceae (B), and Pontederiaceae (in blue) plants.



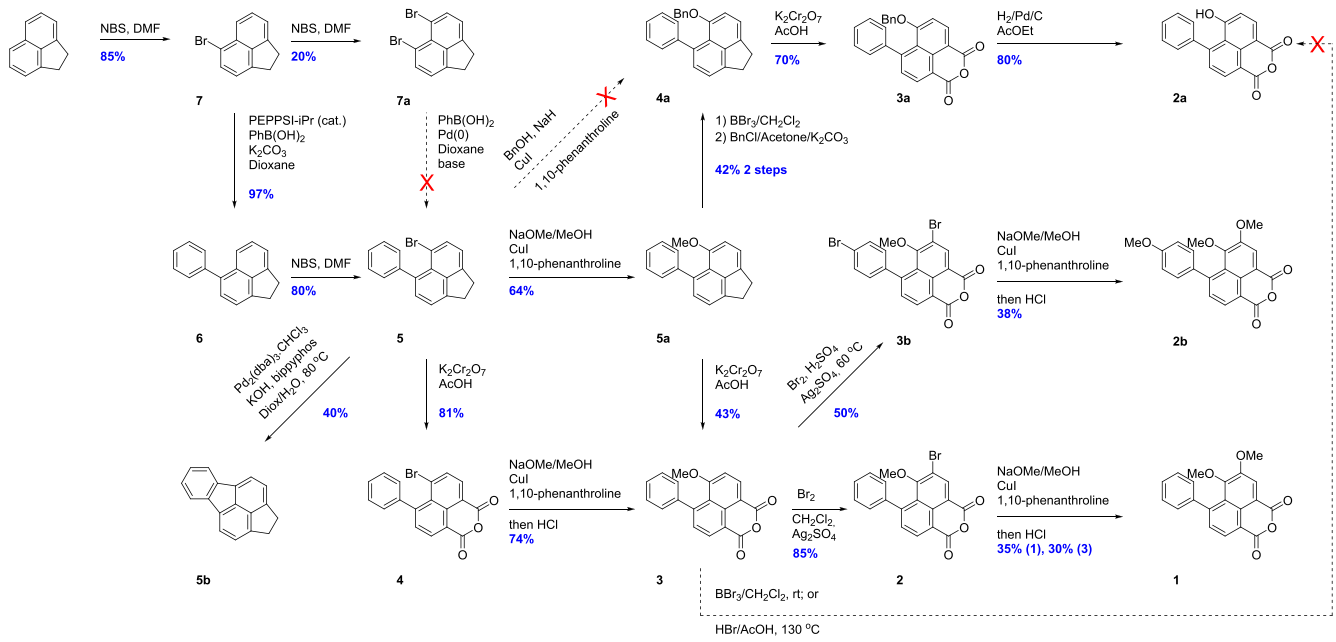

**Scheme 1.** Reported example for generating a phenyl carbamoyl naphthoquinone-type compound from 3,4-dihydroxy-5-phenyl-1,8-naphthalic anhydride [3b].

and phenylboronic acid using PEPPSI-iPr catalysis proceeded smoothly to afford 5-phenylacenaphthene (**6**) in 97 % yield (14 g scale). Treatment of **6** with 1.1 equivalents of *N*-bromosuccinimide delivered the desired 5-bromo-6-phenylacenaphthene (**5**, 15 g scale) in a gratifying 80 % yield. At this point, two permutations in the order of events were possible. Considerations regarding the potential sensitivity of the anhydride group to further transformations encouraged an $S_NAr$- oxidation sequence. Thus, the copper-mediated substitution [7] of **5** with sodium methoxide in methanol afforded 5-methoxy-6-phenylacenaphthene (**5a**) in 64 % yield after column chromatography. Disappointingly, the oxidation of **5a** employing Cr (VI) afforded the corresponding anhydride in only 43 % yield and only after tedious purification. Reconsidering the reaction sequence from **5** led to a modified oxidation-$S_NAr$ proposal (Scheme 3). In this case, it was evident that the methoxide ion could attack the anhydride moiety during the Ullmann-type process. However, a mixture of such methoxycarbonyl-naphthoates could, in principle, participate in the copper-mediated $S_NAr$ substitution with the possibility of regenerating the anhydride group and, therefore, converging to a single product upon acidic workup. Consequently, the microwave irradiation of a mixture of 5-bromo-6-phenylacenaphthene (**5**) and potassium dichromate in acetic acid furnished 4-bromo-5-phenyl-1,8-naphthalic anhydride (**4**) in 81 % yield and suitable purity for the next step without the need for chromatography. Gladly, the copper-mediated substitution of **4** with sodium methoxide in methanol went smoothly, and the cyan-fluorescent 4-methoxy-5-phenyl-1,8-naphthalic anhydride (**3**) was produced in 74 % yield after acidic workup. The bromination of **3** using NBS turned out to be difficult, and only Friedel-Crafts type conditions using bromine and $Ag_2SO_4$ afforded the desired 3-bromo-4-methoxy-5-phenyl-1,8-naphthalic anhydride (**2**) in 85 % yield. The copper-mediated substitution of **2** delivered the target molecule in 35 % yield along with compound **3**, which was recovered in 30 % yield. Attempts to optimize this reaction using different ligands or Buchwald-type reactions failed. Spectroscopic data of the final molecule (**1**) agreed with previous reports [1d].

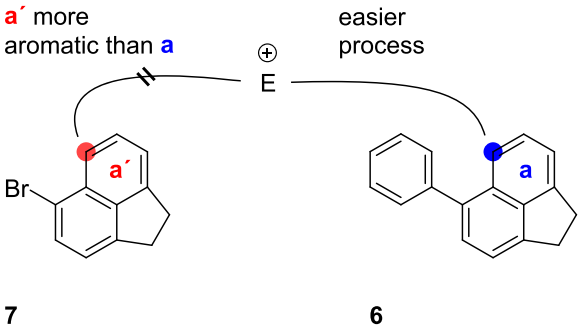
Interestingly, the treatment of **3** with two equivalents of bromine under harsher conditions (sulfuric acid 98 %, 60 °C) allowed the installation of a second bromine atom in position C-4′ of the lateral phenyl ring to produce 3-bromo-5-(4-bromophenyl)-4-methoxy-1,8-naphthalic anhydride (**3b**, 50 % yield). Compound **3b** also participated in a tandem copper-mediated nucleophilic aromatic substitution to provide 3,4-dimethoxy-5-(4-methoxyphenyl)-1,8-naphthalic




**Scheme 2.** Synthetic strategy to prepare 3,4-dimethoxy-5-phenyl-1,8-naphthalic anhydride (**1**).




**Scheme 3.** Synthetic transformations towards **1** and **2a**.




| | *Ring* | |
|---|---|---|
| *Aromaticity index* | a´ | a |
| MCI | 0.03572 | 0.03555 |
| AV1245 | 7.931 | 7.831 |
| HOMA | 0.886 | 0.875 |

**Fig. 2.** Guiding hypothesis for the tactical change leading to compound **5**. MCI: multi-center index; AV1245 (x 1000): Average of the **4c**-multicenter indices along the ring that keep a positional relationship of 1,2,4,5.; HOMA: Harmonic oscillator model of aromaticity.

anhydride (**2b**, 38 %).

With a route to compound **1** established, we attempted to prepare the recently reported 4-hydroxy-5-phenyl-1,8-naphthalic anhydride (**2a**) via demethylation of **3**. Unfortunately, compound **3** resulted impervious to the action of a solution of hydrobromic acid in acetic acid at 130 °C or boron tribromide (1 M) in dichloromethane at room temperature. Attempts to directly substitute the bromine by hydroxyl in anhydride **4** via copper or palladium catalysis also failed. Thus, compound **5** was considered a precursor. Direct substitution of the bromine in **4** using modified Buchwald conditions successful in the synthesis of hydroxyphenalenones [8] afforded 1,2-dihydrocyclopenta[*cd*]fluoranthene (**5b**, 38 % yield) instead of the desired hydroxyphenylacenaphthene (Scheme 3).

The unexpected results forced us to change the nature of the protecting group to prepare compound **2a**. Unfortunately, attempts to directly introduce a benzyloxy group in compound **5** via copper catalysis also failed. Thus, compound **5a** (Scheme 3) was demethylated with $BBr_3$ and benzylated to afford 5-(benzyloxy)-6-phenylacenaphthene (**4a**) in 45 % yield (two steps) and then submitted to standard dichromate oxidation to furnish 4-(benzyloxy)-5-phenyl-1,8-naphthalic anhydride (**3a**) in 70 % yield. Gratifyingly, compound **3a** engaged in hydrogenolysis to provide 4-hydroxy-5-phenyl-1,8-naphthalic anhydride (**2a**) in 80 % yield. The spectroscopic characteristics of compound **2a** matched with the reported natural product [1h].

In summary, a synthesis of 3,4-dimethoxy-5-phenyl-1,8-naphthalic anhydride (**1**) and 4-hydroxy-5-phenyl-1,8-naphthalic anhydride (**2a**) was achieved in seven and eight steps respectively (12 % and 10 % global yield each) starting from acenaphthene. The viability of phenylnaphthalic anhydrides as substrates for copper-mediated (Ullmann-type) $S_NAr$ reactions was demonstrated. Incidentally, difficulties in demethylating methoxynaphthalic anhydrides culminated in a synthesis of 1,2-dihydrocyclopenta[*cd*]fluoranthene and the illustration of the suitability of the benzyl protecting group in chromium-mediated acenaphthene oxidations.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## Acknowledgments

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## Appendix A. Supplementary data

Supplementary data (Experimental procedures. Optimized.xyz coordinates for compounds 5, 6, 7 and 7a. Single-point Hartree-Fock "steric" NBO calculation for compounds **5** and **7a**. $^{1}H$ and $^{13}C$ spectra for all products) to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.154907.

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