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# A Thermal Dehydrogenative Diels–Alder Reaction of Styrenes for the Concise Synthesis of Functionalized Naphthalenes

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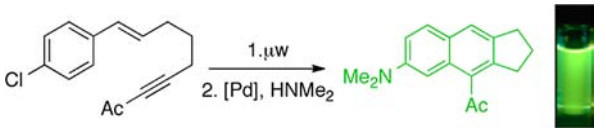
## ABSTRACT




**Functionalized naphthalenes are valuable building blocks in many important areas. A microwave-assisted, intramolecular dehydrogenative Diels–Alder reaction of styrenyl derivatives to provide cyclopenta[*b*]naphthalene substructures not previously accessible using existing synthetic methods is described. The synthetic utility of these uniquely functionalized naphthalenes was demonstrated by a single-step conversion of one of these cycloadducts to a fluorophore bearing a structural resemblance to Prodan.**

Designing and synthesizing small molecules for the purpose of function enables advancement in fields ranging from pharmaceuticals to pesticides.[1] The Diels–Alder (DA) reaction is one of the most powerful and robust transformations for assembling cyclic molecular frameworks, employing a plethora of diene ($4\pi$) and dienophile ($2\pi$) components capable of delivering a rich diversity of cyclic compounds poised for function.[2] One structural variant is the dehydro-Diels–Alder (DDA) reaction, where one, two, or all three of the double bonds of the classic diene and dienophile are replaced with triple bonds, providing access to substituted aromatic compounds not accessible using other chemistries.[3] The energy price to incorporate the high degree of precursor unsaturation required for the formation of aromatic products can be mitigated by the propensity of cyclohexadiene derivatives to aromatize. Aromatic derivatives, in turn, can be prepared from more saturated precursors via a two-step process defined as a *dehydrogenative* DA reaction.[4]

A particularly problematic, but potentially useful, dehydrogenative DA reaction involves the use of styrene as the diene component and an alkyne dienophile, affording a cycloadduct that can aromatize under oxidative conditions to give naphthalene derivatives (Scheme 1).[5]

Problems that can arise when using styrene as the diene range from polymerizations[6] to [2 + 2] cycloaddition reactions.[5a,7] One solution, is to use very reactive dienophiles such as maleic anhydride or benzoquinone. However, the desired cycloadducts are typically obtained in low yields because the reactivity of these dienophiles leads to a second DA reaction with the newly formed diene of the first cycloadduct.[5a] Lack of regioselectivity for the styrenyl DA reaction is also a drawback, which can be overcome by carrying out the reaction intramolecularly.[4a,8] The intramolecular styrenyl DA reaction also suffers from low yields and long reaction times, producing mixtures of dihydronaphthalene and naphthalene products. Even so, the intramolecular Diels–Alder (IMDA) reactions of

(1) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.
(2) Takao, K.-I.; Munakata, R.; Tadano, K.-I. *Chem. Rev.* **2005**, *105*, 4779–4807. Kumar, A. *Chem. Rev.* **2001**, *101*, 1–20. Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176.
(3) Wessig, P.; Muller, G. *Chem. Rev.* **2008**, *108*, 2051–2063.
(4) (a) Ozawa, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 5390–5393. (b) For an example of a dehydrogenative reaction that takes place prior to the Diels–Alder reaction, see: Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892–14895.
(5) (a) For an extensive review on styrenyl Diels–Alder reactions, see: Wagner-Jauregg, T. *Synthesis* **1980**, 769–798. (b) For an early example of styrene as a diene, see: Diels, O.; Alder, K. *Justus Liebigs Ann. Chem* **1926**, *450*, 237–240. (c) For an example employing styrene synthons in Diels–Alder reactions and leading citations, see: Parker, K. A.; Ruder, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 5948–5949.
(6) Stille, J. K.; Chung, D. C. *Macromolecules* **1975**, *8*, 83.
(7) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72*, 4378–4389.

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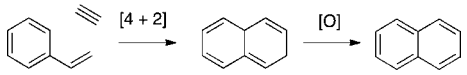
styrenes and electron-deficient alkynes have resulted in the occasional application of this reaction to the synthesis of biologically relevant compounds.[9]

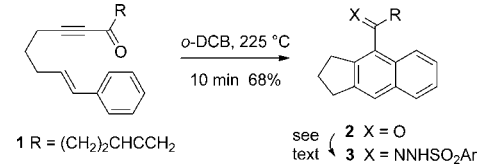
**Scheme 1.** Styrenyl Dehydrogenative DA Reaction




Continued interest in the development of an efficient styrenyl DA reaction is driven by the need for functionalized naphthalene compounds that can serve as valuable building blocks for the synthesis of small molecules in many important areas, such as pharmaceuticals, chiral reagents, liquid crystals, and organic dyes.[10,11] Moreover, the intramolecular styrenyl DA reaction affords a unique functionalization pattern on the resulting naphthalene derivatives that complements other synthetic approaches.[11]

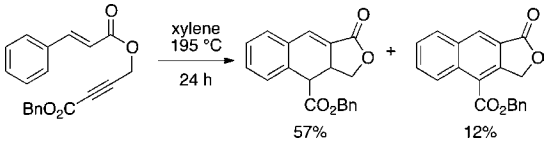
Recently, in our studies directed toward expanding the scope of the thermal [2 + 2] cycloaddition reaction of allene-ynes,[12] we obtained naphthalene **2** and none of the anticipated [2 + 2] cycloaddition product between the allene and the alkyne of **1** upon microwave irradiation in *ortho*-dichlorobenzene at 225 °C for 10 min (Scheme 2)! While the $^{1}$H NMR and $^{13}$C NMR spectra of **2** contained well-defined resonances in the aromatic region diagnostic of a cyclopenta[*b*]naphthalene, verification of the structure of compound **2** was confirmed by an X-ray crystal structure of *para*-toluenesulfonyl hydrazone **3**. The outstanding selectivity of this IMDA reaction for the naphthalene product over the dihydronaphthalene product (1:0), the high yield, and an overall interest in naphthalene derivatives compelled us to study this reaction further.

**Scheme 2.** Dehydrogenative IMDA Reaction



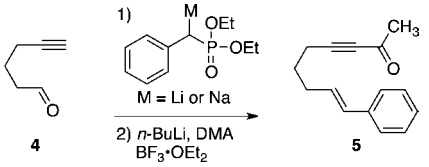

Our investigations differ from other methods for the synthesis of naphthalene derivatives via the IMDA reaction of styrenes, with most of the others sharing a few common features such as 1) the enyne precursors contain either a heteroatom and/or a carbonyl group(s) within the tether (mainly amides and esters); 2) limited functionality on the terminus of the alkyne; 3) reaction conditions requiring high temperatures and long reaction times; and 4) most naphthalene products are contaminated with varying quantities of dihydronaphthalene byproducts (Scheme 3).[13] Moreover, our initial result shows that a TMS group on the terminus of the alkyne is not essential for the exclusive formation of the naphthalene over the dihydronaphthalene product.[4a]

**Scheme 3.** Previously Reported Dehydrogenative IMDA Reaction




A concise synthesis of a dehydrogenative IMDA styrenyl precursor **5** was accomplished in three steps, and in a manner entirely analogous to that used for the preparation of **1** (Scheme 4). Aldehyde **4** is prepared by a PCC oxidation of commercially available 5-hexyn-1-ol in 81% yield. Next, reaction of the lithium salt of diethyl benzylphosphonate with aldehyde **4** affords the styrene moiety of **5** in 68% yield. Deprotonation of the alkyne terminus with *n*-BuLi followed by acetylation of the acetylide produces **5** in 69% yield. For the ensuing IMDA reaction, solvents with lower boiling points were considered because of difficulties in removing high boiling *o*-dichlorobenzene.

**Scheme 4.** IMDA Precursor Synthesis




Microwave irradiation of styrene **5** in either 1,2-dichloroethane (DCE) at 180 °C for 30 min or benzotrifluoride (BTF) at 180 °C for 180 min afforded the cyclopenta[*b*]naphthalene derivative **6** in quantitative yield with no

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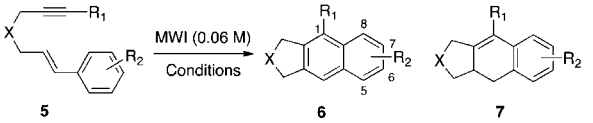
(13) Chackalamannil, S.; Doller, D. O.; Clasby, M.; Xia, Y.; Eagen, K.; Lin, Y.; Tsai, H.-A.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 4043–4047.

**Table 1.** Scope of the Microwave-Assisted Dehydrogenative Diels–Alder Reaction




5 6 7

| entry | 5 | $R^1$ | $R^2$ | X | T (°C) | solvent | t (min) | 6 yield (%)[b] | 7 yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **5a** | $C(O)CH_3$ | H | $-CH_2-$ | 180 | DCE | 30 | 100 (**6a**)[c] | 0 (**7a**) |
| 2 | **5a** | $C(O)CH_3$ | H | $-CH_2-$ | 180 | BTF | 180 | 100 (**6a**) | 0 (**7a**) |
| 3 | **5b** | $C(O)CH_3$ | *p*-Cl | $-CH_2-$ | 180 | DCE | 200 | 100 (**6b**, 7-chloro) | 0 (**7b**) |
| 4[a] | **5c** | $C(O)CH_3$ | *o*-Cl | $-CH_2-$ | 180 | DCB | 180 | 86 (**6c**, 5-chloro) | 0 (**7c**) |
| 5[a] | **5d** | $C(O)CH_3$ | *m*-Cl | $-CH_2-$ | 180 | DCB | 180 | 79 (**6d, 6d'** 6-, 8-chloro) | 0 (**7d**) |
| 6 | **5e** | C(O)Ph | H | $-CH_2-$ | 180 | DCE | 90 | 100 (**6e**) | 0 (**7e**) |
| 7[a] | **5f** | $SO_2CH_3$ | H | $-CH_2-$ | 225 | DCB | 20 | 78 (**6f**) | 0 (**7f**) |
| 8 | **5g** | $SO_2Ph$ | *p*-Cl | $-CH_2-$ | 180 | DCE | 15 | 89 (**6g,** 7-chloro) | 0 (**7g**) |
| 9 | **5h** | SOPh | *p*-Cl | $-CH_2-$ | 180 | DCE | 60 | 75 (**6h,** 7-chloro) | 0 (**7h**) |
| 10 | **5i** | $PO(OEt)_2$ | *p*-Cl | $-CH_2-$ | 225 | DCB | 150 | 100 (**6i**, 7-chloro) | 0 (**7i**) |
| 11 | **5j** | CHO | *p*-Cl | $-CH_2-$ | 180 | DCE | 45 | 83 (**6j**, 7-chloro) | 0 (**7j**) |
| 12 | **5k** | $CO_2CH_3$ | H | $-CH_2-$ | 180 | DCE | 600 | 76 (**6k**) | 0 (**7k**) |
| 13 | **5k** | $CO_2CH_3$ | H | $-CH_2-$ | 225 | DCB | 90 | 97 (**6k**) | 0 (**7k**) |
| 14 | **5l** | $C(O)CH_3$ | H | $-(CH_2)_2-$ | 300 | DCB | 50 | 100 (**6l**) | 0 (**7l**) |
| 15[a] | **5m** | $C(O)CH_3$ | *o*-Cl | $-C(CO_2Et)_2-$ | 180 | DCB | 30 | 100 (**6m,** 5-chloro) | 0 (**7m**) |
| 16[a] | **5n** | C(O)Ph | H | –O– | 180 | DCE | 30 | 28 (**6n**) | 15 (**7n**) |
| 17 | **5o** | $C(O)CH_3$ | H | –NTs– | 180 | DCE | 10 | 30 (**6o**) | 56 (**7o**) |
| 18[a] | **5p** | $C(O)CH_3$ | *o*-Cl | –NTs– | 180 | DCB | 10 | 24 (**6p,** 5-chloro) | 48 (**7p**) |
| 19[a] | **5p** | $C(O)CH_3$ | *o*-Cl | –NTs– | 225 | DCB | 10 | 59 (**6p,** 5-chloro) | 6 (**7p**) |

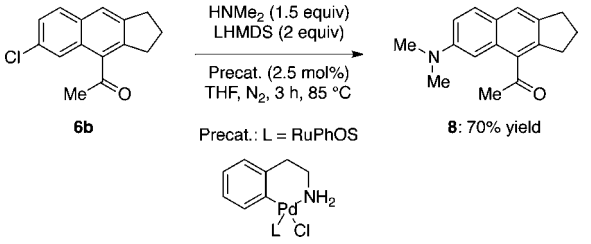
[a] Yields are reported after flash chromatography on silica gel. [b] Crude yield, but no impurities by $^1H$ NMR. [c] When purified by filtration through a silica gel plug, **6a** was obtained in 95% yield.

additional purification required of the final product (entries 1 and 2, Table 1). It is interesting to note that heating **5b** conventionally in a sealed tube at 180 °C required 48 h for the reaction to complete. With conditions for an efficient and high yielding IMDA reaction utilizing a lower boiling solvent in hand, we turned our attention to scope and limitations investigations. First, substitution on the aryl group was examined; exchanging a hydrogen atom for a chlorine atom was deemed valuable, enabling access to a wide-range of naphthalene derivatives via Pd-catalyzed cross-coupling reactions. Moreover, Cl-atom is more stable and accessible than other halides or groups used for coupling, such as triflates. Styrenyl derivatives **5b**, **5c**, and **5d** were prepared and subjected to microwave irradiation. The *p*-chlorostyrene **5b** gave 7-chloronaphthalene **6b** in quantitative yield after 200 min (entry 3). The *o*-chlorostyrene **5c** also produced only one product, the 5-chloronaphthalene **6c** in 86% yield, even though two products are possible (entry 4). The *m*-chlorostyrene **5d** gave a 1.4:1 mixture of the 6-chloro- and 8-chloronaphthalenes, **6d** and **6d′** in 79% yield (entry 5).

Next, a number of functional groups on the terminus of the alkyne were investigated in the IMDA reaction. Substitution of the alkyne with a phenyl methanone gave the cycloadduct **6e** in quantitative yield after 90 min (entry 6). Reaction scale did not affect the yield of this reaction, but it did have an effect on the reaction time; for example, 50 mg of **5e** afforded **6e** in 90 min, while 200 mg of **5e** required a reaction time of 130 min. Placement of the methylsulfonyl and phenylsulfonyl groups on the terminus of the alkyne to produce **5f** and **5g** resulted in a facile IMDA reaction to give **6f** and **6g** in 78% and 89% yield, respectively (entries 7 and 8). Sulfoxide **5h** gave a slightly lower yield but still afforded the naphthalene product **6h** selectively (entry 9). Similarly, the diethyl phosphonate substituted alkyne **5i** produced **6i** in quantitative yield in 150 min (entry 10). Alkynal **5j** affords the naphthalene **6j** in 83% yield in 45 min (entry 11). A substrate with a methyl ester on the alkyne terminus, **5k**, slowed the reaction considerably, requiring 600 min to obtain complete conversion to **6k** in 76% yield (entry 12). The reaction time could be shortened from 600 to 90 min by heating to 225 °C in *o*-dichlorobenzene; this also resulted in an improved yield for **6k** of 97% (entry 13).

Finally, structural changes in the tether were examined. Extending the tether by one methylene unit gave precursor **5l** that required heating at 300 °C for 50 min in *o*-dichlorobenzene but provided tetrahydroanthracene **6l** in quantitative yield (heating at 225 °C for 240 min resulted in recovery of starting material). To the best of our knowledge, this is the first successful styrenyl IMDA reaction using a four-atom tether to provide a naphthalene fused to a six-membered ring. Reaction of the precursor **5m** with an all-carbon tether possessing a diester moiety afforded only **6m** in quantitative yield in 30 min (entry 15). Next, an ether tether was used to connect the styrene and the alkyne. The cycloaddition of **5n** was complete in 30 min and gave a 2:1 ratio of the naphthalene **6n** to the dihydronaphthalene **7n** (entry 16). The toluenesulfonamide substrate **5o** also afforded a mixture of products, but in a 2:1 ratio of the dihydronaphthalene **7o** to naphthalene **6o** in 10 min in a combined yield of 86% (entry 17). The case of the toluenesulfonamide tether with a chloro group on the aromatic ring also provided a 2:1 ratio of the dihydronaphthalene **7p** to naphthalene **6p** in 10 min in a combined yield of 72% (entry 18). When **5p** was heated to 225 °C for 10 min, nearly

**Scheme 5.** Palladium-Catalyzed Cross Coupling Reaction of **6b** To Afford Fluorophore **8**




a 10:1 ratio of naphthalene **6p** to dihydronaphthalene **7p** was obtained in 65% yield (entry 19). For each of the heteroatom-containing tethers, a mixture of products was observed; furthermore, when the reaction time was extended to 120 min for entry 19, the ratio of naphthalene **6p** to internal standard did not change, but the dihydronaphthalene **7p** was no longer evident by $^1$H NMR, suggesting that dihydronaphthalene **7p** is not converted to **6p**. Separation of dihydronaphthalene **7p** and naphthalene **6p** could not be accomplished by column chromatrography, so attempts were made to oxidize the mixture to **6p** using cerric ammonium nitrate (CAN), dichlorodicyanobenzoquinone (DDQ), Pd/C, or $O_2$. All reactions gave either complete decomposition of the naphthalene and dihydronaphthalene products or selective decomposition of the dihydronaphthalene.[8d]

We envision these naphthalene derivatives as potential candidates for application to the ever-increasing field of small molecule fluorescent probes.[14,15]

Consequently, reaction of **6b** to a palladium-catalyzed amination reaction using RuPhos precatalyst, lithium hexamethyldisilylazide (LHMDS), and *N*,*N*-dimethylamine afforded cyclopentanaphthalene **8** in 70% yield (Scheme 5).[16,17] Compound **8** was strongly fluorescent with an absorption maximum of 377 nm and an emission maximum of 510 nm. The emission maximum was significantly red-shifted from the structurally similar Prodan, which has an emission maximum of 440 nm in dichloromethane.[18] Moreover, a quantum yield of 99% was measured for compound **8** in dichloromethane.[19] In conclusion, a microwave-assisted, dehydrogenative Diels–Alder reaction affords 13 different, functionalized naphthalenes in excellent yield. Our study represents the first intramolecular dehydrogenative DA reaction between styrene and electron-deficient alkynes to produce functionalized naphthalenes without contamination with the dihydronaphthalene product, for the all-carbon containing tethers.

For the heteroatom-containing tether, dihydronaphthalenes were obtained along with the naphthalene products. Investigations are underway to understand the mechanism by which these two products are formed. Finally, we have demonstrated the synthetic utility of this method by preparing a highly fluorescent dye **8** that possesses other interesting photophysical properties (see Supporting Information for more details).

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**Supporting Information Available.** Detailed experimental procedures and characterization data are available for all compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.